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CORRIGENDA.

P. 186, l. 9. *For Fig. 1 read Figs. 1 and 2.*

P. 186, l. 7 from bottom. *For $x = (c + \alpha F)w$ read $x = (c - \alpha F)/w$.*

P. 189, l. 9 from top. *For $x = c_0 x_0 - (1 - c_0)x_w$
read $x = c_0 x_0 + (1 - c_0)x_w$.*

THE SYSTEMS PHENOL-GLUCOSE- β -PENTACETATE, PHENOL-CELLOBIOSE- α -OCTACETATE, AND *p*-NITROPHENOL-CELLOBIOSE- α -OCTACETATE.

BY RALPH J. B. MARSDEN, JAMES M. BAINBRIDGE AND
ALFRED MORRIS.

Received 21st August, 1942.

It has been suggested by one of us¹ that the swelling action of phenol on cellulose acetates is due, in part at least, to the formation of a hydrogen-bond complex between the phenol and the cellulose acetate. Unfortunately the nature of cellulose acetates prevents this point being tested directly by any of the usual criteria for compound formation, and though there is evidence from infra-red absorption measurements of a hydrogen-bond compound between phenol and ethyl acetate² the similarity between ethyl acetate and a cellulose acetate is not very pronounced, and the evidence is again not very direct.

An attempt has therefore been made to fill this gap by examining by means of freezing-point determinations the phase relationships existing between phenol and *p*-nitrophenol on the one hand, and glucose- β -pentacetate and cellobiose- α -octacetate on the other. These last two compounds were chosen as being readily characterisable, reasonably accessible, and to be regarded as the two lowest members of the cellulose acetate series.

The system phenol-glucose- β -pentacetate resolved itself into a simple two component system with a single eutectic. There was no hint of anything which by phase-rule criteria could be interpreted as indicating any compound formation.

Results for the systems containing cellobiose- α -octacetate were not so simple in interpretation, as undoubtedly some decomposition took place at the higher temperatures, *i.e.* in the ester-rich mixtures, though this was minimised, especially when *p*-nitrophenol was being used, by melting the phenol first and adding the ester to it. While not so unambiguous as that involving the glucose ester, the system phenol-cellobiose octacetate is also apparently a simple one; certainly there is no strong evidence of compound formation at any of the simpler ratios. The ester-rich side of the system is not quite so certain as the rest of it, owing to the slight amount of decomposition mentioned.

Because of its greater swelling activity towards cellulose acetate and the theoretical grounds for believing it to be more prone to form hydrogen-bond complexes than phenol, *p*-nitrophenol was also investigated.¹ With cellobiose octacetate there is definite evidence for at least two compounds of nitrophenol-ester ratios 2 : 1 and 1 : 2, though incipient decomposition again makes the ester-rich side of the system somewhat unreliable at high temperatures. Of these two compounds, the one formed from two nitrophenol molecules and one ester molecule can certainly be explained by a hydrogen-bond structure, and it is also the compound for whose existence the evidence is most precise.

¹ Marsden and Urquhart, *Shirley Inst. Mem.*, 1942, 18, 121; or *J. Text. Inst.*, 1942, 33, T 105.

² Gordy and Niclson, *J. Chem. Physics*, 1938, 6, 12.

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TABLE I.
THE SYSTEM PHENOL-GLUCOSE- β -PENTACETATE.

Weight composition % phenol	100.0	80.3	77.0	70.4	65.2	50.2	53.5
Molecular composition %	100.0	97.0	93.2	90.4	88.7	81.8	82.6
Freezing point °C. . .	41.05	38.05	29.85	25.0	18.5	7.0	1.15
Weight composition % phenol	51.0*	50.2	41.6	33.0	20.5	10.2	0.0
Molecular composition %	81.8	81.0	74.0	67.0	51.7	31.0	0.0
Freezing point °C. . .	--4.8	2.05	30.25	50.0	87.5	115.2	131.8

* Synthetic mixture of eutectic composition predicted by the other results.

TABLE II.
THE SYSTEM PHENOL-CELLOBIOSE- α -OCTACETATE.

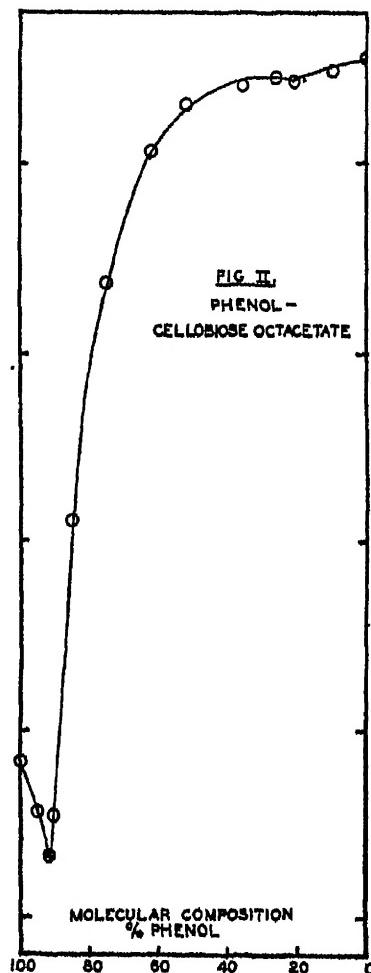
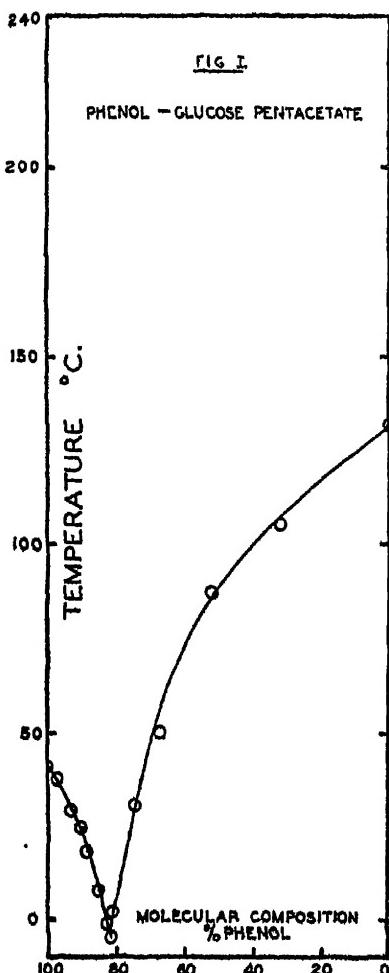
Weight composition % phenol	100.0	73.0	60.2	56.0	43.6	20.3	18.4
Molecular composition %	100.0	95.0	91.5	90.2	84.8	75.0	62.0
Freezing point °C. . .	41.05	28.55	16.7	27.15	105.55	108.6	203.2
Weight composition % phenol	11.3	7.0	4.6	3.5	1.5	0.0	
Molecular composition %	52.0	35.4	26.0	20.7	9.8	0.0	
Freezing point °C. . .	213.6	220.75	222.75	221.75	224.5	227.75	

TABLE III.
THE SYSTEM *p*-NITROPHENOL-CELLOBIOSE- α -OCTACETATE.

Weight composition % nitrophenol .	100.0	95.4	89.6	83.6	76.4	69.4	61.9	58.5
Molecular composition % nitrophenol .	100.0	99.0	97.5	96.5	94.0	91.0	88.8	87.3
Freezing point °C. . .	113.85	112.85	111.4	108.4	104.8	98.8	91.0	91.0
Weight composition % nitrophenol .	54.0	52.8	50.3	45.9	38.9	29.9	26.0	25.9
Molecular composition % nitrophenol .	85.1	84.5	83.1	80.5	75.7	67.5	63.2	63.0
Freezing point °C. . .	98.8	107.8	119.4	133.8	157.4	173.8	167.4	152.6
Weight composition % nitrophenol .	24.4	22.9	19.1	13.6	6.4	6.0	5.5	4.8
Molecular composition % nitrophenol .	61.4	59.2	53.6	43.5	31.6	24.0	22.4	19.7
Freezing point °C. . .	150.6	153.5	173.0	200.5	210.4	203.5	207.5	208.4
Weight composition % nitrophenol .	4.3	3.6	3.5	3.2	2.4	2.2	1.7	0.0
Molecular composition % nitrophenol .	17.7	15.3	15.0	14.0	10.9	10.0	7.5	0.0
Freezing point °C. . .	209.4	212.5	198.5	205.0	214.0	212.5	215.5	227.75

Formulation of the other compound is much more difficult, but scarcely affects the argument on which it was hoped that this investigation would shed light.

It does thus appear that under favourable conditions complexes can be formed between phenols and members of the cellulose acetate series. Whether such complexes are due to the existence of hydrogen bonds is



of course not proved, but they can most reasonably be formulated upon such a hypothesis. Although this clarifies matters to some extent, it does not dispose of the problem as to what degree of association between two molecules is to be defined as "compound formation," as it seems probable that association which is definite from the standpoint of infrared spectra is not necessarily definite enough for it to be manifest from freezing-point data.

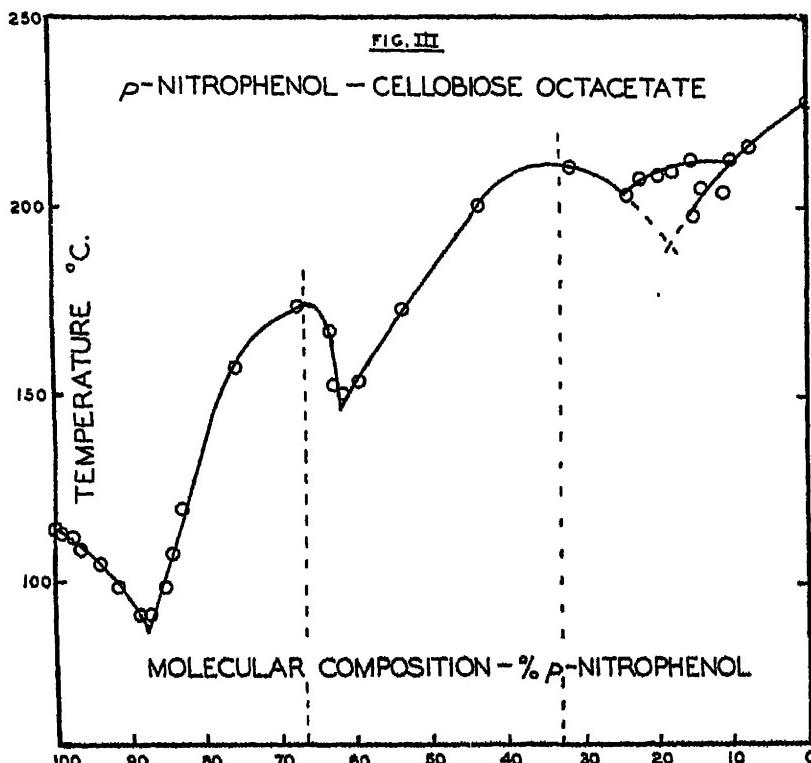
4 THE SYSTEMS PHENOL-GLUCOSE- β -PENTACETATE, ETC.

Experimental.

Preparation of Materials.

Glucose- β -pentacetate was prepared from pure glucose ("for intravenous use") by treatment with acetic anhydride and fused sodium acetate. The product was re-crystallised from alcohol, m.p. $131\cdot8^\circ\text{C}$. (corr.).

Cellobiose- α -octacetate was prepared from filter paper according to the method of Haworth and Hirst,² the product being recrystallised successively from alcohol, isopropyl acetate, and alcohol containing a little dilute aqueous ammonia to ensure complete freedom from traces of sulphuric acid. M.p. $227\cdot75^\circ\text{C}$. (corr.).



Both these esters were recovered from melts with phenol by careful extraction of the phenol with large quantities of dilute aqueous ammonia, the solid ester residue being repeatedly recrystallised from alcohol until a constant melting-point was obtained.

Phenol was used directly from a freshly opened bottle of "Phenol 40/41° B.P. Detached Crystals" supplied by May & Baker, Ltd. M.p. found $41\cdot05^\circ\text{C}$. (corr.).

p -Nitrophenol was purified from a commercial sample by recrystallisation from hot distilled water containing a trace of hydrochloric acid, the product being dried on a porous tile. M.p. $113\cdot85^\circ\text{C}$. (corr.).

Freezing Point Determinations.

These were done in the usual Beckmann apparatus, with the precaution of passing a gentle stream of dried air into the centre of the tube carrying the stirrer, with the object of preventing the ingress of moisture. For freezing points above room temperature the apparatus was used with one air jacket and a draught shield, but when freezing mixtures were required a second air jacket was added and the draught shield dispensed with.

Owing to the limited supplies of materials available, many of the mixtures were made up by dilution of a previous mixture by the appropriate compound, but entirely fresh mixtures were made up in any case where decomposition was suspected.

The values of freezing-points given in the tables of results are the mean of the results obtained from at least two cooling curves obtained with each individual mixture. All temperatures are corrected for emergent stem errors.

These results are illustrated by Figs. 1, 2 and 3.

While these results are not quite as complete or conclusive as had been hoped, it has not been deemed profitable to pursue the matter further under present circumstances.

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THE HYDROGEN BOND AND THE HYDRATION OF ORGANIC MOLECULES.

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Received 2nd October, 1942.

In the steady development in recent years of the theory of the solubility of non-electrolytes relatively little attention has been directed to binary liquid systems one component of which is water and the other an organic substance. It has long been recognised, of course, that the strong tendency of water molecules to associate with one another through hydrogen bonds is primarily responsible for the small mutual miscibility of water and many organic solvents, and that other factors usually play by comparison a secondary part. Such factors are the nature of the field of force surrounding the organic molecule, its polarity and polarisability, and its shape, in so far as this will affect the packing of the molecules in the liquid into which the water molecules are to be inserted. If, however, the molecules of the organic substance contain atoms or groups possessing some specific attraction for water, the miscibility of the two liquids is greater than it would be in the absence of those atoms or groups. Sometimes such hydration of the organic substance may produce a new type of molecule. Thus, a carbonyl compound might form a hydrate containing the group $>\text{C}(\text{OH})_2$. But a more general possibility is that the two molecules become linked by a hydrogen bond, the bonding hydrogen atom being provided in some cases by the water, in others by the organic molecule. The influence which such hydrogen

¹ *Solubility*, Reinhold Publishing Corp., New York, 1936, pp. 149, 166; *Science*, 1936, 83, 21.

THE HYDRATION OF ORGANIC MOLECULES

bond formation can have on the mutual miscibilities of water and organic liquids has been pointed out by Hildebrand.¹ These solubility effects are so pronounced when hydrogen bond formation is strong as to suggest that information about rather weaker association of this type might be obtained from suitable solubility studies.

The object of the experiments to be described was to investigate by solubility measurements the association of water molecules with those of organic substances of various chemical types. Neither the solubilities of water in the pure organic solvents or the solubilities of the latter in water seem to afford satisfactory criteria on which to base conclusions about the hydration of the organic molecules. The former measure the extent to which the relatively small water molecules can enter the rather loosely held structure of larger organic molecules, while the solubilities of the organic substances in water depend on how easily the bulky organic molecules can be inserted in a somewhat tightly held network of water molecules. The shape of the organic molecules and their properties other than any tendency they may have to form hydrates might therefore play rather an important part in determining the reciprocal solubilities with water and render it almost impossible to assess the extent of hydration if this were small. A more satisfactory method of approach seems to be to measure the solubility of water in dilute solutions of the various organic substances in a non-polar solvent such as benzene, and then to compare the initial increases in the solubility of water in benzene (expressed as a mole fraction) brought about by these substances. The question of the structure of the liquid organic compound does then not arise. The solubility of water in benzene is small, and if we make the not unreasonable approximation that at a given temperature the concentration of the water present as such in a saturated solution is not affected by the presence of small amounts of a third substance, then we may ascribe any increase in the solubility of the water to the formation of a hydrate of the added substance. The initial slope of the curve obtained by plotting the increase in the solubility of water against the concentration of the added organic substance may then be regarded as a measure of the fraction of the molecules of the organic substance which, in a very dilute benzene solution saturated with water, exists in the form of hydrated molecules. These hydrated molecules are in equilibrium with monomeric water molecules, since water dissolved in benzene has been shown by freezing-point studies to be unassociated.² This method of studying the hydration of organic substances has the further advantage that direct comparison can be made both with substances solid at ordinary temperatures and also with those liquids with which water is miscible in all proportions.

So far little work has been done on these lines. Bell³ has measured the solubility of water in dilute solutions of mono-, di-, and tri-chloracetic acids in benzene. Several ternary liquid systems of which water and benzene are components have been investigated, but the data for the solubility of water in dilute solutions of the third component are usually scanty and rather inaccurate. In the experiments described in this paper the effect of six organic substances on the solubility of water in benzene was measured. The compounds selected were aniline, dimethylaniline, anisole, nitrobenzene, chloroform and bromobenzene. Benzene was chosen as the non-polar solvent as its physical properties make it particularly suited to the experimental method used. In particular, it appears to dissolve more water than any other non-polar liquid (a point to be discussed more fully later), and the desired solubilities, though small, can accordingly be measured more accurately.

¹ Peterson and Rodebush, *J. Physic. Chem.*, 1928, 32, 709.
² *Z. physik. Chem. A*, 1930, 150, 20.

Experimental.

The solubility of water in benzene and in dilute benzene solutions of the above-mentioned substances was determined by the synthetic method according to the procedure adopted by Grosschult.⁴ About 50 c.c. of the benzene solution were introduced into a clean dry glass tube about 3·5 cm. in diameter with a narrow inlet, a small amount of water was added from a weight pipette, and the tube at once sealed off. It was then agitated at a sufficiently high temperature until all the water had gone into solution, placed in a bath of water, and allowed to cool slowly. The temperature at which the benzene solution was saturated with respect to the aqueous phase was taken to be that at which opalescence appeared, rather than the temperature at which the opalescence disappeared on warming the tube again, since the aqueous phase usually showed a tendency soon after its appearance to form a film on the walls of the containing vessel. The temperature at which the clear liquid became opalescent was reproducible to within 0·3° C.

Benzene was dried over sodium wire until fresh wire remained un-tarnished over a period of several days, and then distilled either from sodium powder or from a liquid sodium-potassium alloy. Samples of benzene obtained in these two ways gave identical solubility results. Bromobenzene and chloroform were dried over phosphorus pentoxide, aniline and dimethylaniline over potassium hydroxide, and anisole and nitrobenzene over anhydrous calcium chloride. All of these substances were fractionated after drying in an all-glass apparatus, and thereafter kept out of contact with atmospheric moisture. The dry benzene and the solutions made up from it were preserved in flasks closed with phosphorus pentoxide tubes.

Results.

Table I gives the values obtained for the solubility of water in benzene solutions of the six substances studied, and in benzene itself. Each substance was investigated at two concentrations. S is the number of grams of water dissolved at 7° C. by 1000 g. of a benzene solution of the concentration specified. Thus, at 21·0° C., 1000 g. of a solution containing 43·27 g. of nitrobenzene were found to dissolve 0·508 g. of water.

For every solution studied and for benzene alone, the logarithm of the solubility of water was found to vary linearly with the reciprocal of the absolute temperature within the limits of experimental error. Lines were fitted by the method of least squares to the experimental points plotted in this way, and values for the solubility of water at any desired temperature derived from them. Table II gives the interpolated values for the solubility of water at 25° C. (expressed as mole fractions) together with the mean error for each value. (The mean error represents the average deviation of the individual points of the series concerned from the least square line.)

The extrapolated value for the solubility of water in benzene at 20° C. is 0·570 ± 0·007 g. per 1000 g. solution. The more recent values for this quantity are 0·608⁵; 0·601⁶; 0·573⁷; 0·55⁸; 0·53⁹; 0·50.¹⁰ The average error in all our solubility determinations was about 2%.

⁴ Z. Elektrochem., 1911, 17, 348.

⁵ Hill, J. Amer. Chem. Soc., 1923, 45, 1143.

⁶ Bell, J.C.S., 1932, 2903.

⁷ Kohnbaum and Walton, J. Amer. Chem. Soc., 1930, 52, 3568.

⁸ Tarassonkov and Poloshinewa, Ber., 1932, 65, 184.

⁹ Miyake, Mem. Coll. Eng. Kyushu Univ., 1931, 6, 1.

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TABLE I

Nitrobenzene.				Aniline.				Dimethylamine.			
$\frac{1.327 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{1.095 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{1.011 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{1.465 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{2.011 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{1.198 \text{ gm.}}{1000 \text{ gm. soln.}}$	
S	T	S	T	S	T	S	T	S	T	S	T
0.508	21.0	0.600	15.1	1.237	35.7	2.157	25.8	0.910	31.3	0.547	
0.780	25.1	0.787	25.0	1.430	39.8	2.174	32.7	1.213	33.0	1.047	
1.073	33.7	1.083	33.2	1.586	43.0	3.323	15.0	1.378	15.1	1.842	
1.073	47.5	1.031	41.2	2.282	51.7	1.114	97.8	1.671	53.1	2.727	
2.390	10.0	2.145	53.0	3.040	73.0	5.006	70.0	2.200	61.1		
2.448	60.5	2.649	61.0			6.351	72.0				

Chloroform.				Bromobenzene.				Anisole.				Solubility in Pure Benzene.
$\frac{1.645 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{2.201 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{1.181 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{1.001 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{1.241 \text{ gm.}}{1000 \text{ gm. soln.}}$		$\frac{2.617 \text{ gm.}}{1000 \text{ gm. soln.}}$		
S	T	S	T	S	T	S	T	S	T	S	T	
0.607	21.5	0.928	35.2	0.557	19.9	0.448	16.4	0.420	19.3	0.792	22.8	0.643
1.026	37.1	1.764	50.1	0.851	33.8	0.838	34.3	1.213	37.4	0.970	30.0	1.213
1.198	39.5	2.478	62.9	0.927	37.0	1.285	48.6	1.501	45.4	1.561	11.0	1.206
1.683	53.4	3.052	68.0	1.106	43.5	1.668	56.3	2.084	54.6	2.260	55.3	1.610
2.204	59.5			1.281	44.6	2.315	68.7	2.505	61.7	2.698	61.6	2.073
		1.526	50.5									2.100
		1.839	57.5									38.5
		2.409	60.8									24.70
												71.0

TABLE II

Substance.	Mole Fraction of added Substance.	Solubility of Water (Mole Fraction $\times 10^3$).		Increase in Solubility of Water (Mole Fraction $\times 10^3$).
		209 ± 74 .		
(Pure Benzene.)	—			
Nitrobenzene .	0.02781	3.24	1 0.13	0.25 1 0.17
	0.1000	3.43	1 0.10	0.04 1 0.20
Aniline . .	0.04250	3.74	1 0.07	0.75 1 0.11
	0.1545	8.07	1 0.23	5.98 1 0.27
Dimethylaniline	0.06748	3.07	1 0.04	0.08 1 0.13
	0.1148	3.48	1 0.04	0.40 1 0.08
Chloroform . .	0.03075	3.05	1 0.11	0.06 1 0.15
	0.1552	2.98	1 0.07	- 0.01 1 0.11
Bromobenzene . .	0.07934	3.01	1 0.06	0.02 1 0.10
	0.175	3.12	1 0.05	0.13 1 0.06
Anisole . .	0.0856	3.42	1 0.03	0.13 1 0.07
	0.1398	3.82	1 0.07	0.83 1 0.17

Discussion.

In Fig. I are plotted the data given in Table II for aniline, nitrobenzene, anisole and dimethylaniline. The size of the circles round the points for these substances gives the magnitude of the experimental error in each case. The results for bromobenzene and chloroform have not been re-

presented, since, within the limits of experimental error, these substances clearly have no effect on the solubility of water in benzene in the concentration range studied. The figure also includes the data in the literature for phenol,¹⁰ methyl alcohol,¹¹ ethyl alcohol,¹² and acetic acid.¹³ The curves shown for these substances have been drawn with due regard for other points which, on the scale chosen, lie outside the figure. Bell¹⁴ has measured the solubility of water in dilute benzene solutions of mono-, di-, and tri-chloracetic acids. His results (not represented in Fig. 1) show that, as for acetic acid, there is for each of these acids a linear relation between the increase in the solubility of water and the acid concentration. The line becomes progressively more steep on passing from acetic to tri-chloracetic acid, until with this last substance the molar ratio of the increase of the solubility of water to the concentration of the acid is unity.

Fig. 1 shows clearly that the compounds having the largest initial effects on the solubility of water in benzene are the hydroxyllic substances and aniline, that is compounds containing a hydrogen atom capable of linking the molecule with one of water. It

therefore appears that hydrogen bonds involving water molecules are stronger when the oxygen atom of the water acts as an acceptor for the hydrogen atom of the other molecule, than when the bonding hydrogen atom is derived from the water molecule. It is interesting to note that the solubility of water in benzene is initially increased more by phenol than by methyl or ethyl alcohol, in spite of the fact that water and liquid phenol are only partially miscible below 66°C. Although

the conditions for hydrogen bond formation have by no means been precisely defined, there appears to be a rough parallelism between the acidity of a hydrogen atom and its readiness to form such a bond. The stronger association between phenol and water than between alcohol molecules and water is therefore presumably due to the greater acidity of the phenol. This compound also has a larger initial effect on the solubility of water in benzene than the still more acidic acetic acid. It must be remembered, however, that even at low concentrations acetic acid in benzene is predominantly in the form of double molecules, and though the experiments of Bell¹⁴ indicate that both the single and double molecules

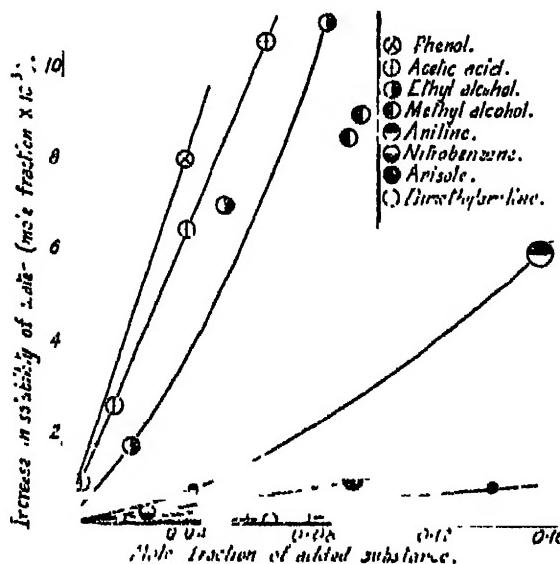


FIG. 1.

¹⁰ Horiba, *Mem. Coll. Sci. Kyoto Imp. Univ.*, 1914, I, 49.¹¹ Barbaudy, *Compt. Rend.*, 1926, 182, 1279.¹² Barbaudy, *Rev. Trav. Chim. Pays-Bas*, 1926, 45, 207; Washburn, Hinrichs and Vold, *J. Amer. Chem. Soc.*, 1931, 53, 3237.¹³ Waddell, *J. Physic. Chem.*, 1898, 2, 233; cf. ref. 3.¹⁴ Bell and Arnold, *J.C.S.*, 1935, 1432.

of a carboxylic acid can be hydrated, the degrees of hydration of the two species will almost certainly not be the same. It is not possible to assess the degree of hydration of single molecules of acetic acid in benzene solution, a knowledge of which is necessary for proper comparison with other substances, nor should it be forgotten that in this case union of the acid and water molecules may possibly be due not to hydrogen bond, but to formation of the molecule $\text{CH}_3\text{C}(\text{OH})_2$.

Independent evidence for strong association between the molecules of hydroxylic substances and water in benzene solution has been obtained from freezing-point studies on solutions of phenol, ethyl alcohol,¹³ and trichloracetic acid¹⁴ in aqueous benzene.

The limiting slope of the curve for dimethylaniline is nearly zero. This we interpret to mean that the nitrogen atom in this amine has almost no tendency to act as an acceptor for the hydrogen atom of a water molecule, so that the association of aniline with water is probably due to bonding through the hydrogen atoms of the amino-group. It is worth noting, however, that the solubility of monohuorodichloromethane in dimethylaniline has been found to be greater than the ideal,¹⁵ showing that the nitrogen atom can form a bond with the hydrogen of a haloform molecule. It appears to be increasingly doubtful that the hydrogen bond can be satisfactorily interpreted on a simple electrostatic basis, or whether the only factors determining its strength are the acidity of the hydrogen atom and the size and electronegativity of the acceptor atom. If this were so, then in view of the well-known strong bond formation between chloroform and ether we should expect to find evidence for comparably strong association between chloroform and water, for since the dipole moment of water is greater than that of ether the effective negative charge on the oxygen atom can scarcely be less for water than ether. As, however, chloroform at low concentrations has no effect on the solubility of water in benzene, we conclude that the tendency to hydration is very feeble or non-existent.

The results for nitrobenzene indicate that there is some hydration of this substance, which might have been expected in view of the well-known ability of nitro-groups and hydroxyl groups, as in *o*-nitrophenol, to associate by means of a hydrogen bond. Anisole molecules are likewise capable of hydration, but to a rather less extent.

Bromobenzene at low concentrations has no measurable influence on the solubility of water in benzene, which shows that the presence in an organic molecule of polar linkages is not in itself sufficient to bring about any marked attraction for water molecules.

It is interesting that the solubility of water in benzene, though small, is considerably higher than that in any other non-polar solvent for which there is reliable data. Taking in each case what seems the most trustworthy value afforded by the literature, the solubility of water (expressed as its mole fraction $\times 10^4$) at 20° C. in benzene is 2.46; in tetrachloroethylene¹⁷ 0.63; in carbon tetrachloride⁷ 0.73; in cyclohexane⁸ 0.5; in carbon disulphide¹⁸ 1.06. (The figure for tetrachloroethylene has been calculated from the concentration of water in this solvent when in equilibrium with the salt hydrate pair $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O} \rightleftharpoons \text{Na}_2\text{SO}_4$). While it would be quite unjustifiable on this fact alone to postulate some kind of specific attraction between the molecules of water and benzene, an enquiry into certain properties of suitable binary mixtures of which benzene forms one component has led us to the conclusion that some weak attraction does actually exist, and that other molecules containing a hydrogen atom capable of forming a hydrogen bond may associate, though rather feebly,

¹³ Rozsa, *Z. Elektrochem.*, 1911, 17, 934.

¹⁴ Zellhoeffer, Copley and Marvel, *J. Amer. Chem. Soc.*, 1938, 60, 1337.

¹⁵ Bell, *J.C.S.*, 1932, 2905.

¹⁶ Clifford, *Ind. Eng. Chem.*, 1921, 13, 628; Uspanaki, *Petroleum Ind.*, 1929, 17, 713.

with benzene molecules. One of the most striking examples of such association comes from Simons' work¹⁹ on the partial pressure of hydrogen fluoride in benzene solution. At high concentrations he found the large positive deviations from Raoult's Law which are to be expected for a mixture of two substances with such dissimilar molecules. At low concentrations of hydrogen fluoride, however, its partial pressure is considerably less than it would be if Raoult's Law were obeyed, which can only mean that there is some association of the two compounds. There are unfortunately almost no data on the solubility of hydrogen fluoride in other non-polar solvents, but Simons found it to be nearly twenty times more soluble in benzene than in octane. Another simple molecule capable of taking part in hydrogen bond formation is that of ammonia, which, like water, is more soluble in benzene (on a mole fraction basis) than any other non-polar solvent.²⁰

There is evidence of other kinds that hydroxylic substances such as phenol can associate in some way with benzene. For solutions of phenol in benzene, the absorption band characteristic of the hydroxyl group of the monomeric phenol molecules has been found to occur at an abnormally low frequency. This has been interpreted as being due to association of phenol and benzene molecules,²¹ which is also suggested by the low value of 2.4 kg. cal. reported recently²² for the strength of the hydrogen bond formed between two phenol molecules in benzene solution. Determinations of the bond strength in media other than benzene have yet to be made, but an approximate estimate of its magnitude in liquid phenol itself can be obtained from a comparison of the heat of evaporation of liquid phenol with those of other aromatic substances which are not associated but the molecules of which have nearly the same shape and dipole moment as phenol. The molar heat of evaporation of phenol at its melting-point (calculated from vapour pressure data) is approximately 17 kg. cal. (It decreases rather rapidly as the temperature rises, owing, no doubt, to decreasing association). At this temperature the molar heats of evaporation of chlorobenzene and bromobenzene are about 9 and 10 kg. cal. respectively. (These substances have been selected for comparison since they are about as polar as phenol, but other unassociated benzene derivatives with one small substituent have molar heats of evaporation of very much the same magnitude.) How many hydrogen bonds are broken for each mole of phenol evaporated is not known, but if (as seems probable) the molecules in liquid phenol are linked in chains of indefinite length, the average number cannot be more than one per molecule, though it may be less. A rough estimate of the strength of the hydrogen bond between two phenol molecules in liquid phenol is therefore between 7 and 8 kg. cal., and though this may be in error by 2 or 3 kg. cal., it is so much greater than the 2.4 kg. cal. found for the bond strength in benzene solution as to suggest that this last quantity is the energy evolved when a dimeric phenol molecule is formed not from two free single phenol molecules but from two phenol molecules each solvated in some way by benzene.

It is well known that the hydrogen atom in the chloroform molecule can take part in hydrogen bond formation with certain substances, and it is therefore interesting to find evidence which indicates that chloroform and benzene have a slight tendency to associate with one another. For example, the two liquids mix with the evolution of heat, which amounts to 1.58 cal. for the addition of one gm. of chloroform to one of benzene at 18° C., and the partial vapour pressures of the two substances in a mixture of them are a little less than they would be were the solution ideal.²³

¹⁹ *J. Amer. Chem. Soc.*, 1931, 53, 83.

²⁰ Bell, *J.C.S.*, 1931, 7371.

²¹ Badger, *J. Chem. Physics*, 1940, 8, 283.

²² Lassettre and Dickinson, *J. Amer. Chem. Soc.*, 1939, 61, 54.

²³ Linchbarger, *J. Amer. Chem. Soc.*, 1895, 17, 615; Schulze, *Z. physik. Chem.*, 1921, 97, 388; Hirabayashi, *J. Phys. Sci. Tokyo* (1), 1925, 1, 155; Schmidt, *Z. physik. Chem.*, 1926, 121, 231.

Chloroform appears to be the only liquid which mixes exothermally with benzene, with the exception of the similar substance pentachlorethane, mixtures of which with benzene also show negative deviations from Raoult's Law.²¹ The solubility in benzene of triphenylmethane, the molecule of which is in some ways not unlike that of chloroform, is 32.4 mole. per cent. at 20° C. That this is considerably greater than the ideal value of 22.0 mole. per cent. is evidence for intermolecular association which is of a particularly interesting kind, since both substances contain only carbon and hydrogen.

The facts summarised here show that the benzene molecule can sometimes associate with other molecules which contain a hydrogen atom capable of forming a hydrogen bond. It is therefore suggested that the higher solubility of water in benzene compared with its solubility in other non-polar solvents is to be attributed to a rather weak attraction which opposes the other factors tending to cause separation into two liquid phases. A difficulty arises in trying to formulate more precisely the way in which the benzene molecule acts as an acceptor for the hydrogen atom, since hydrogen bond formation has hitherto been regarded as being possible only when the acceptor molecule contains a strongly electronegative atom with an unshared pair of electrons. If a carbon atom in the benzene ring were to acquire such a pair of electrons the electronic symmetry of the ring would be destroyed, and it seems improbable on energetic grounds that the benzene molecule is brought into such an abnormal condition on association. It is possible, however, that the electronegative centre of attraction for the hydrogen atom is not one of the carbon atoms but the centre of the benzene ring, where the combined action of the six carbon atoms symmetrically disposed about it might build up a small but appreciable electron density, especially if the Dewar structures contribute to some extent to the actual condition of the molecule.²² The hydrogen atom responsible for the association may be imagined to approach the nucleus along the line through the centre normal to the plane of the ring. It will then be nearer to the centre of the ring than to any one carbon atom, and at the distance to which it is permitted by repulsive forces to approach the carbon atoms it may be experiencing attractive forces from the centre of the ring. Association of the two molecules in this way will therefore be essentially of the dipole-induced dipole type.²³

In view of what has been said of the ability of the benzene molecule to associate with certain other molecules, it would seem that this substance is not the best solvent in which to study such properties of hydrogen bonds as their strength and effect on infra-red absorption spectra. The qualitative deductions made earlier in this paper about the relative extents to which the molecules of different substances are hydrated in benzene solution are not affected, however, though if it be conceded that there is some slight attraction between the molecules of water and benzene, then for substances like chloroform and bromobenzene, which at low concentrations neither increase nor decrease the solubility of water in benzene, it would be better to say that the tendency of water to associate with them is no greater than that with benzene, rather than that they are not hydrated at all.

Summary.

It has been shown that information about the hydration of molecules of organic substances can be obtained by studying the effect of these substances at low concentrations on the solubility of water in a non-polar

²¹ Weissenberger, Schuster and Pamer, *Ber. Akad. Wiss., Kl. IIb*, 1925, 134, 287.

²² Pauling and Wheland, *J. Chem. Physics*, 1933, 1, 362.

²³ Moelwyn-Hughes and Shetman, *J.C.S.*, 1936, 101.

solvent. Six compounds have been examined in benzene solution in this way. The results, together with those given in the literature for other substances, have been discussed with relation to the nature of the hydrogen bond and the conditions governing its formation.

It has been pointed out that water is several times more soluble in benzene than in any other non-polar liquid. In the light of other evidence, it is concluded from this that the molecules of water and benzene have a slight tendency to associate with one another.

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THE MECHANISM OF PHASE CHANGE IN SOME IRON-SILICON ALLOYS.

By H. LIPSON AND A. R. WEILL.

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The equilibrium diagram of the iron-silicon alloys has proved to be much more evasive than the early work on it seemed to promise. Phragmen,¹ by means of an X-ray study, had outlined the main details of the diagram and they were supported by the more accurate work of Haughton and Becker.² The iron-rich end of the diagram proposed is shown in Fig. 1. Apart from one disturbing feature—the apparent contact of the solidus and liquidus at 14% Si—there seemed to remain only the necessity for more precise determinations of small parts of the diagram.

The X-ray work of Stoughton and Greiner³ showed that the position was not so simple. In Fig. 1 the limiting α solid-solution above 1030° C. is in equilibrium with a phase ϵ and below 1030° C. with a phase η . Stoughton and Greiner found that at a much lower temperature the η phase is unstable; and they suggested that at 825° C. there is a eutectoid reaction by which η decomposes again into $\alpha + \epsilon$. This is incorporated in their diagram, part of which is shown in Fig. 2.

This is an unusual feature in an equilibrium diagram. It is, of course, essentially similar to the $\alpha-\gamma-\delta$ change in pure iron, but this also is unusual, and it was thought worthy of close attention.

In the present work, the changes that take place in the X-ray powder pattern of a 25% silicon alloy annealed at 720° C. have been observed, and they prove that η does tend slowly to disappear at this temperature. In the course of the observations a rather remarkable method for the change of phase was found to occur. A description of this and a possible theoretical explanation of it are the main subjects of this paper. The theory is one that may be of general application to the study of phase transformations; it affords a basis for Ostwald's Law⁴ of successive reactions and suggests a possible limitation of this law.

¹ Phragmen, *J. Iron Steel Inst.*, 1926, 114, 394.

² Haughton and Becker, *Ibid.*, 1930, 121, 315.

³ Stoughton and Greiner, *Metals Handbook*, p. 396 (American Soc. Metals, Cleveland, 1939).

⁴ Findlay, *The Phase Rule and its Applications*, p. 60 (Longmans, Green & Co., London, 1923).

The Crystal Structures Involved.

In order to describe the methods used, a brief description of the crystal structures of the α , ϵ and η phases must be given. The crystal structures have also some bearing on the details of the equilibrium diagrams proposed by the various workers.

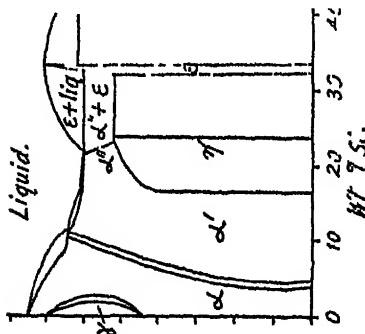


Fig. 1.—Iron-rich part of iron-silicon diagram after Haughton and Becker (1930).

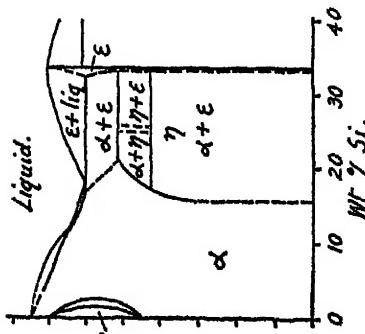


Fig. 2.—Iron-rich part of iron-silicon diagram after Sponton and Greiner (1939).

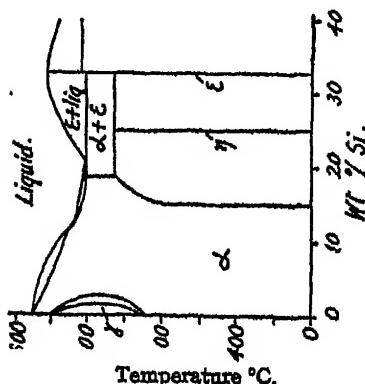


Fig. 3.—Iron-rich part of iron-silicon diagram after Osawa and Murata (1940).

Phase α is a solid solution of Si in Fe. At low temperatures the phase boundary is near the composition Fe₅Si and the atomic arrangement is that typified by the alloy Fe₃Al; at high temperatures more Si can go into solution and the ordering of the atoms follows the same course as in the Al-Fe system although it does not approach the composition FeSi. Osawa and Murata¹ have suggested that the ordering is responsible for the apparent contact of the solidus and liquidus as found by Haughton and Becker; in their diagram they show the ordered solid solution formed by a peritectic reaction between the liquid and the disordered solid solution (Fig. 3). While this is not the usual result of ordering in other alloy systems, it is similar to the state of affairs in the solution of Al in Ni;² in this the ordered and disordered solid solutions are separated by a two-phase gap. The two-phase gap proposed by Osawa and Murata, however, is so narrow that it is difficult to find experimentally.

Phase ϵ has a cubic structure which has been determined by Phragmen;³ it is confined almost exactly to the composition FeSi.

The structure of η has not yet been determined. Osawa and Murata⁴ say that it is hexagonal with $a = 6.727$ Å, $c = 9.411$ Å. In the present investigation, however, it was

found that the photographs, taken in a 19 cm. diameter camera⁵ with Co $K\alpha$ radiation, could be completely indexed with a " $\bar{\epsilon}$ " axis of only half this length. This is supported by the fact that nearly all the l indices

¹ Bradley and Jay, *Proc. Roy. Soc., A*, 1932, 136, 210.

² Osawa and Murata, *Nippon Kinzoku Gakkaishi*, 1940, 4, 228.

³ Alexander and Vaughan, *J. Inst. Metals*, 1937, 61, 247.

⁴ Bradley and Taylor, *Proc. Roy. Soc., A*, 1937, 159, 56.

⁵ Bradley, Lipsom and Petch, *J. Soc. Instr.*, 1941, 18, 216.

given by Osawa and Murata are even; those that are odd belong to lines that are found to be $K\beta$ lines, or to lines that have not been observed in the present work.

The dimensions found for the unit cell are: $a = 6.734 \text{ \AA}$, $c = 4.703 \text{ \AA}$. The density is 6.1 g./c.c. , and since the composition is known to be about 40 atomic per cent. Si there must be 16 atoms in the unit cell. It is therefore not possible to fit the atoms into the unit cell in the ratio 3:2 as the usually accepted formula of the η phase would demand. The nearest possibility is 5:3. Thus the crystallographic evidence would point to the composition Fe_5Si_3 (23.1 % Si) as the correct composition of the η phase, instead of Fe_3Si_2 (25.0 % Si). In view, however, of the large number of instances, such as CuAl_2 ¹⁰ in which crystallographically equivalent positions are not filled by similar atoms, this evidence of the composition of the η phase cannot be taken as conclusive.

The only possibly significant absences of X-ray spectra are 0001 and 0003. This would suggest that the space-group is either C_{6_3} , $C_{6_3}2$ or $C_{6_3}m$, C_{6_3} being the most probable.

Experimental Methods.

The alloys were made in a high-frequency induction furnace, the components being Hilger iron F603 (99.97 % Fe) and silicon of purity 99.85 % from the Electro Metallurgical Co. (Niagara). They were annealed at 1120° C. for two days *in vacuo* to eliminate coring and allowed to cool in the furnace. Powders for X-ray examinations were obtained by crushing small pieces of the alloys.

The results to be described were obtained on an alloy containing nominally 25 % Si. The powder from it, without further heat treatment, contained a large amount of η and some α and ϵ . It was found to be rather difficult to get consistent results by quenching this powder from different temperatures, and so it was decided to follow the changes in the powder by annealing for different periods of time and then quenching. In this way, although equilibrium may not be attained it might be possible to see which way the reaction was proceeding.

Accordingly several samples of the three-phase powder were sealed into evacuated silica tubes, and these were annealed together at 720° C. This is about 100° C. below the reaction temperature proposed by Stroughton and Greiner, but high enough, it was thought, for the changes to proceed reasonably quickly. At intervals a tube was withdrawn from the furnace and dropped into cold water. An X-ray photograph of the powder was then taken.

The proportions of the phases present were measured by photometry of the X-ray photographs. A characteristic line from each phase was chosen, subject to the following conditions: first, each line must be one that stood clear from any others of its own or of either of the other two patterns; secondly, the three lines must be reasonably close together on the film so that their relative intensities should not be greatly dependent on the size and shape of the specimen;¹¹ and thirdly, each line must be a reasonably strong one on its own pattern so that small amounts of the phase can be measured. The three lines chosen were: for α , 220; for ϵ , 421; for η , 5034. From these lines the proportions were found by comparison with the lines from an artificial mixture of equal weights of the pure phases obtained from other alloys.

By these methods each phase can be recognised definitely and the changes followed quite clearly. The accuracy, however, is not high; the estimation of intensities, even in more favourable cases,¹² involves

¹⁰ Stockdale, *J. Inst. Metals*, 1933, 52, 111.

¹¹ Bradley, *Proc. Physic. Soc.*, A, 1935, 47, 879.

¹² Petch, *J. Iron Steel Inst.*, *in press*.

errors of several per cent. and since a standard specimen had to be used there is a possibility of systematic errors.

Results.

The results are given in Table I and are shown diagrammatically in Fig. 4. As a check on these results the composition of the alloy was worked out from each photograph, with the assumption that the α phase contained 1.60 % Si; η , 23.1 % Si, and ϵ , 33.4 % Si. The composition should, of course, be constant, and it will be seen in the last column that it does lie within 1.3 % of the nominal composition. It is rather disturbing that the variation is systematic,

TABLE I.—CHANGES IN THE PROPORTIONS OF PHASES IN 25 % SI ALLOY WITH TIME OF ANNEALING AT 720° C.

Time.	Percentages.			Calculated Si %.
	α	η	ϵ	
2½ hours	21	55	24	—
4 " "	0	69	31	26.3
8 " "	27	30	43	25.6
17 " "	31	26	43	25.3
2 days	43	17	40	24.2
4 " "	51	7	42	23.9
1 week	51	4	45	24.1
2 weeks	50	0	44	24.6
4 " "	53	0	47	24.2
8 " "	55	0	45	23.8

but in view of the assumptions involved and in the possibility of systematic errors, perhaps it is not surprising. The chemical analysis of the alloy gave 24.2 % Si, but it is difficult to see how the proportions of the phases could be explained on this basis; and the alloy is rather difficult to analyse on account of its chemical inertness.

The changes in the proportions of the phases are quite different from what was expected. It was thought that, if η were unstable at 720° C., its amount should gradually decrease with time; actually its amount increased at first and then began to decrease. The α phase behaved in a still more remarkable way: its amount first decreased to zero and then increased gradually, at the expense of η . The reaction was very slow, and η was still detectable after eight weeks' annealing, although its amount was too small to measure.

An attempt was made to repeat these changes, but it was found difficult to reproduce exactly the initial conditions. However, the general trend of the changes remained the same.

The same alloy has been examined at different temperatures, although

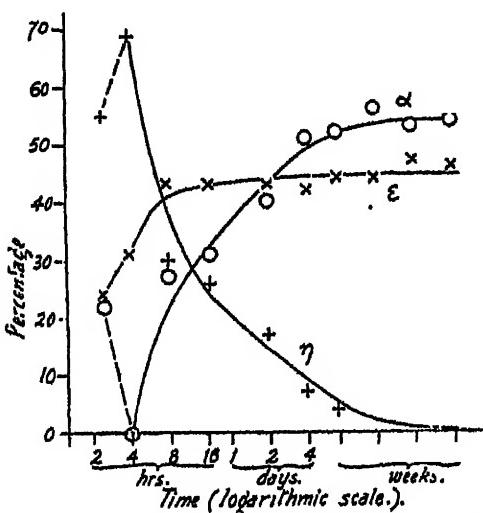


FIG. 4.—CHANGES IN THE PROPORTIONS OF PHASES WITH TIME.

not in such detail, and the initial disappearance of the α phase has been found to occur at the lowest temperature we have used, 550° C.

In alloys less rich in Si the α phase does not disappear; in a 17.0% Si alloy, for instance, the α phase changes directly to the final composition. This is evidenced by the appearance of diffraction lines corresponding to the larger spacing, less Si, which gradually increase in strength while the initial ones decrease. There is no gradual shift of the diffraction lines, which would be the case if the composition of the α phase changed continuously.

Discussion.

Since the η phase tends to disappear on annealing at 720° C. the present results support the diagrams that give it as unstable at this temperature. Nevertheless, its decomposition is so slow that it is not surprising that the earlier workers thought that η was stable down to room temperature.

The initial changes, however, seem difficult to understand. Some light can be thrown on them by applying the principle of lowest free energy,^{13, 14} for, although free energies themselves cannot be evaluated, some of the general properties they must have to produce the observed

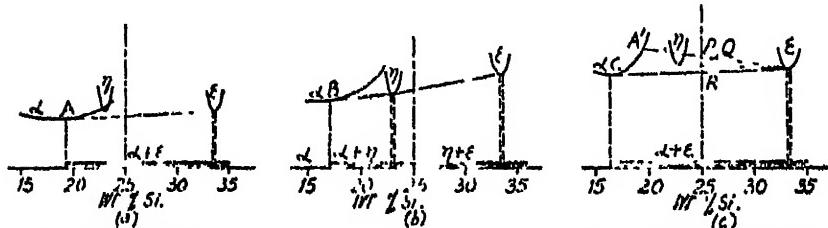


Fig. 5.—Hypothetical free-energy curves for the different phases (a) above 1030° C.; (b) 1030° — 825° C.; (c) below 825° .

equilibrium diagrams may be postulated. For instance, the free-energy curves of η and ϵ must have pronounced minima, as shown in Fig. 5, in order to produce narrow phase-fields of invariant composition; but the free-energy curve for α must have less curvature in order to account for the variation of the phase boundary with temperature.

Above 1030° C. the relative dispositions of the free-energy curves must resemble those shown in Fig. 5a; the η curve lies wholly above the common tangent to the α and ϵ curves, so that η always has a higher free energy than a mixture of α and ϵ . η is stable between 1030° C. and 825° C. because its free-energy curve cuts the common tangent to the α and ϵ curves, as shown in Fig. 5b. Below 825° C. the η curve has moved relatively upwards again, as shown in Fig. 5c, so that η is again unstable. The only difference between Figs. 5a and 5c is that the relative dispositions and shapes of the α and ϵ curves have changed so that the common tangent to them touches the α curve at C, 16.0% Si, at the lower temperature, instead of A, about 19% Si, at the higher.

If the alloy is quenched from the higher temperature the α phase, A, is retained. But this will not give the lowest free energy since it is represented by the point A' in Fig. 5c. The free energy of the 25% Si alloy, as a mixture of α and ϵ , will be represented by the point P on the

¹³ Rozeboom, *Z. physik. Chemie*, 1899, 30, 385.

¹⁴ Lipson and Wilson, *J. Iron Steel Inst.*, 1940, 142, 107.

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line through A' and the minimum of the ϵ curve. This line will not, of course, go exactly through the minimum, but as the ϵ curve is sharp it will do so approximately. On annealing, the free energy must change to the value given by the point R. It could, of course, do this directly by converting some of the α to ϵ , thereby impoverishing the α or Si so that its composition changed to the point C. If, however, the η curve comes below the line A'P, as it must do at least just below the eutectoid temperature, 825°C ., there is a state of intermediate free energy, represented by the point Q. To achieve this state α reacts with ϵ to form η ; to achieve the state of lowest free energy the η then dissociates into $\alpha + \epsilon$.

This method of change is similar to that observed, and so it would appear that the free energy prefers to change in discrete steps rather than in one complete step or continuously, provided that structures are possible that provide the intermediate values of free energy. Until free energies can be calculated as functions of atomic arrangement it will not be possible to know when such structures exist, and so to test the generality of these conclusions; but that other cases occur is shown by the existence of Ostwald's Law of successive reactions. This states that "when a system passes from a less stable condition it does not pass directly into the most stable of the possible states, but into the next more stable, and so step by step into the most stable." Since "the most stable" means "that with the lower free energy," this law is seen to be a generalisation of the conclusion arrived at in this paper. The approach from the standpoint of free energy, however, suggests an important limitation. At the temperature of transition from one form to another the two forms must have the same free energy; thus there cannot be any intermediate values. Therefore Ostwald's Law should apply only if the high-temperature modification is held at a temperature much below that of the transition, so that the free-energy differences are large enough for intermediate values to occur.

Summary.

The equilibrium diagram of the system Fe—Si is considered in the light of crystallographic evidence, and it is concluded in agreement with previous workers that the phase η dissociates into $\alpha + \epsilon$ by both a peritectoid reaction at 1030°C . and a eutectoid reaction at 825°C . The changes of the proportions of phases present in an alloy quenched from above the higher temperature when it is annealed below the lower one have been investigated by X-ray methods; it is found that the original α phase disappears and is then replaced by the final one, which has a different silicon content.

A possible reason for this, based on free-energy differences, is given.

The authors wish to thank Professor Sir Lawrence Bragg and Dr. A. J. Bradley for their interest in this work and for their encouragement. They wish also to acknowledge the kind interest of the Controller of Research and Development, Ministry of Supply, by whose permission this paper has been published.

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RATES OF PYROLYSIS AND BOND ENERGIES OF SUBSTITUTED ORGANIC IODIDES (PART I).

By E. T. BUTLER AND M. POLANYI.

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There is much evidence of an indirect nature, in the wide variation in reactivity of related organic compounds, which suggests that the nature of a chemical bond is greatly influenced by substitution. This would seem to conflict with the additivity rule of Bond Energies based on thermochemical evidence, which assumes that the energy of a given kind of bond is a constant. The present work was begun with the object of clarifying this situation by observing the effect of substitution on organic bond strength as manifested in the rates of pyrolysis of a series of organic iodides.*

R. A. Ogg and Ogg and Polanyi have studied the pyrolysis of a number of aliphatic iodides by static methods.¹ Under their conditions the kinetics of the decomposition are rather complex, and we have come to the conclusion from our own work reported below, that the rate of the primary bond breaking process $RI = R + I$ cannot be deduced correctly from their results. Pyrolysis as a means of establishing bond energies was used by Rice and Johnston² who measured the temperature coefficients of the rates of decomposition of several organic compounds and calculated the corresponding activation energies. They used a flow method in which the free radicals formed during the process were allowed to remove metallic mirrors. We used a similar arrangement for pyrolysing organic iodides, while measuring the rate of reaction by the amount of iodine (and in certain cases the hydrogen iodide) formed. The advantages of the flow method are twofold: by the accumulation of the product resulting from an extended period of flow it is possible to use

* A preliminary communication of our results was made in *Nature*, 1940, 146, 121.

How far we have, here, succeeded in establishing the correct values of bond-energies may be open to doubt. However, the confirmation which our results for $(Cl_3- -I)$ and (C_2H_5-I) have recently gained by quite independent observations (see p. 20 and p. 35 below); the close correspondence of the variations of estimated bond-strength with predicted forms of resonance; the theory which could be built up on this basis for the variations of formation heats and the accompanying changes in dipole strength for a series of hydrocarbons and their derivatives; the correspondence between estimated bond energies and activation energies of the Na-reaction—all those features together have convinced us that we may be permitted to disregard for the time certain gaps in the kinetic evidence of the pyrolysis experiments. Nevertheless, we would have preferred to extend this evidence before publication—especially as this would have saved much tiresome discussion of details—if the extension were at all possible. However, the experiments had to be discontinued in consequence of the war for an indefinite time and postponement of their publication would involve a serious risk of their complete loss. In view of the variety of subjects on which they seem to throw light, we have felt their publication in the present form to be desirable.

¹ Ogg, *J.A.C.S.*, 1934, 56, 526; Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, 31, 604; see also Jones and Ogg, *J.A.C.S.*, 1937, 59, 1931, 1939, 1942; Jones, *Ibid.*, 1938, 60, 1877; 1939, 61, 3284.

² Rice and Johnston, *Ibid.*, 1934, 56, 214.

very large volumes of gas in the reaction and thereby (a) maintain very small partial pressures of the organic substance, and (b) limit the total decomposition to a very small percentage. The low concentrations of the initial and final products thus achieved reduce considerably the chances of secondary reactions. These are suppressed further by the brief duration of the reaction which is over in a second or less as the gas passes through the reaction chamber.

Experimental.

The complete apparatus is illustrated in Fig. 1. The reaction vessel R_1R_2 was of Pyrex, R_1 being 6 cm. in diameter and R_2 2 cm., each being 15 cm. long. It was possible to heat either the whole vessel R_1R_2 (volume 440 c.c.) or the narrow part R_2 (40 c.c.) alone, and in this way a tenfold variation in contact time could be effected without changing the rate of flow; adjustment of the latter gave further variation of contact time.

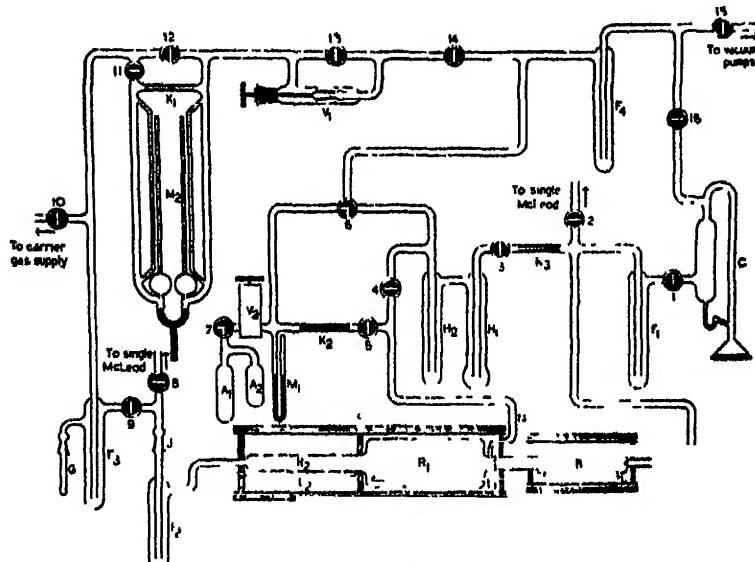


FIG. 1.

The temperature of the reaction vessel was measured by means of copper-advance thermocouples placed in the narrow inlet tubes L_1 and L_2 . When steady conditions had been attained the maximum difference in temperature along the whole length of the reaction vessel was 10° at 500° , and less at lower temperatures. The average temperature inside the reaction vessel was found by moving the thermocouples along the tubes and reading the temperatures at 1 cm. intervals. By careful control the temperature could be kept constant within $\pm 1.5^\circ$ during a run of several hours duration.

The carrier-gas stream was circulated by the three-stage mercury vapour pump C. After removal of mercury vapour by passage through the liquid air trap F, the stream divided into two parts. One part went first through the vessel B (where mercury was introduced in those experiments in which its effect was investigated) and entered the reaction vessel through a short capillary, while the other part after picking up the vapour of the organic iodide entered the reaction vessel at N. The decomposition products and undecomposed iodide were condensed in F_1 and F_2 , immersed in a mixture of acetone and solid CO_2 and liquid air respectively. The

rate of flow of the carrier-gas was measured by the pressure gradient across the calibrated capillary K_1 recorded on the double McLeod gauge M_1 , and could be varied by adjustment of the Hauschild valve V_1 .

Two methods were employed for controlling and measuring the rate of entry of the iodide into the reaction vessel. Iodides of high vapour pressure (> 20 mm. at room temperature) were introduced into the storage vessel A_1 and outgassed by freezing and evacuating several times. The iodide vapour flowed through the needle valve V , the fine capillary K , and the tap 5 into the carrier gas stream. The flow of the iodide was controlled by adjusting V , and measured by the fall in pressure across K_1 , which was calibrated for each iodide used. Iodides of lower vapour pressure were introduced by a method devised by Warhurst.³ The stream of carrier-gas passed first through the trap H_1 containing the iodide and then through a second trap H_2 , maintained at a temperature about 20° below that of H_1 . This arrangement ensured saturation of the carrier gas with the iodide at the temperature of H_2 . The rate of flow of the iodide was again found by preliminary calibration.

Before beginning a run the reaction vessel was baked out for two hours at a pressure less than 10^{-6} mm. When the compound undergoing pyrolysis gave hydrogen iodide as well as free iodine, the latter was condensed in F_2 at -78° , while the former passed through F_1 and collected in F_3 at -195° . At the end of the experiment F_2 was cut off, the contents washed out with absolute alcohol and the iodine titrated against standard sodium thiosulphate. The hydrogen iodide was titrated against standard alkali. When mercury was present, the mercury halides collected in F_3 were (after removal of the volatile contents of the trap) reduced by boiling with zinc dust and water and the iodide estimated with standard silver nitrate.

The ethyl, *n*-propyl, *n*-butyl and allyl iodides were commercial products, carefully purified before use, while the other iodides were prepared and purified by standard methods. Cylinder nitrogen was freed from oxygen by passage over sodium at 350° , and cylinder hydrogen was purified by passage through a palladium thimble. Pure nitric oxide was made by the method of Giauque and Johnston.

Results.

In Table I are presented the results for ethyl iodide in hydrogen as carrier-gas. We will discuss to begin with only the experiments carried out at 492° - 494° . The rates of reaction are expressed in terms of "first order constants" k_1 ; which must not prejudice the question of the actual kinetic mechanism involved. Comparison of the pairs grouped together shows that except in one case reproducibility was better than $\pm 5\%$. In view of the whole investigation we may say that this degree of reproducibility within one run is not uncommon where the quantities of iodine produced are sufficient. However in some cases, to which attention will be called in due course, reproducibility was considerably less.

The introduction of Hg -vapour which was used from Expt. 3 onwards had no noticeable effect. This admixture was continued throughout the experiments with ethyliodide and then left away. A more than twofold increase in H_2 pressure in Exps. 3-4 and 9-10 produced a rise of k_1 by about 40 %, while a more than sixfold increase in Exps. 13-14 and 11-12 caused a rise of k_1 by 115 %. In the latter comparison we disregard the change in ethyliodide pressure since in subsequent experiments its variation proved entirely ineffective. Comparing (with the same proviso) Exps. 9-10 and 14-13 we note a considerable fall of k_1 with increasing time of contact.

The tendency for k_1 to rise with increasing pressure and to fall with increasing contact time was much less noticeable—in fact, not definitely

³ Warhurst, *Trans. Faraday Soc.*, 1939, 35, 674.

TABLE I

Exp. No.	Temp °C	Total Pres. mm	Iodide Pres. mm $\times 10^{-3}$	Contact Time sec.	k_p $(\text{cc}^{-1} \times 10^{-8})$	k_{int} $(\text{cc}^{-1} \times 10^{-8})$
1. Ethyl Iodide in Hydrogen.						
NO { 1	492	5.05	1.40	0.275	4.02	
11g { 2	492	6.40	1.21	0.256	4.07	
3	493	5.71	1.22	0.264	5.00	
4	492	5.02	1.21	0.265	4.01	
10	493	13.1	1.07	0.252	6.00	
10	493	14.1	1.02	0.256	6.77	
11g { 13	493	13.3	8.11	0.580	3.35	
11g { 14	492	13.2	9.33	0.660	3.70	
11	493	2.06	1.30	0.647	1.52	
12	493	2.02	1.21	0.659	1.52	
6	462	6.90	1.04	0.260	1.37	
7	462	5.56	1.18	0.202	0.82	
8	461	5.52	1.21	0.304	0.90	
2. Ethyl Iodide in Nitrogen.						
Varying iodide pressure { 27	495	12.8	1.47	1.30	1.10	1.02
26	493	13.3	1.64	1.04	1.22	—
30	493	9.32	30.4	1.60	1.00	1.07
29	494	9.58	33.5	1.76	1.06	0.98
Varying total pressure { 15	493	1.79	1.75	1.61	0.87	—
17	494	4.92	1.56	1.56	0.95	—
18	493	5.01	1.52	1.52	0.93	—
19	493	9.00	2.17	1.92	0.90	—
Varying contact time { 28	494	13.3	1.54	2.33	1.07	0.97
20	492	12.8	1.43	1.72	1.08	—
25	492	12.5	1.50	0.728	1.69	—
22	494	12.7	1.38	0.641	1.67	—
24	493	12.4	1.57	0.740	1.32	—
31	494	10.7	26.4	0.130	0.50	0.63
23	492	11.8	1.52	0.660	1.04	—
NO present { 32	493	9.48	31.7	1.74	1.00	0.80
33	493	9.45	30.9	1.60	2.00	0.85
3(a). n-Propyl Iodide in Nitrogen.						
112	492	6.50	23.7	1.08	4.94	4.32
109	492	6.28	11.0	0.576	5.20	3.69
108	491	7.32	8.21	0.473	5.10	3.47
113	492	6.12	11.2	0.0412	3.69	6.01
115*	493	6.06	11.0	0.548	5.35	4.14
114†	492	5.71	15.7	0.710	5.38	5.01
110	440	6.96	10.0	0.521	0.466	0.408
111	442	6.39	10.2	0.550	0.472	0.444
* NO present. † Carrier-gas : hydrogen.						
3(b). n-Butyl Iodide in Nitrogen.						
121	492	6.49	6.32	1.40	8.08	11.2
125	491	5.39	7.78	0.365	8.38	—
118	492	6.63	2.57	0.502	10.05	17.4
122	492	6.36	7.38	0.0435	7.30	14.0
119	440	7.01	7.59	0.506	0.83	2.30
120	440	6.53	2.85	0.568	0.59	1.44
124	441	6.54	8.28	0.646	0.65	0.99

TABLE I.—Continued.

Exp. No.	Temp. °C.	Total Press. mm.	Iodide Press., mm. $\times 10^{-3}$.	Contact Time, sec.	k_1 , sec. $\times 10^3$	k_{III} ,
4(a). Allyl Iodide in Nitrogen.						
76	494	6.14	50.2	0.520	160.0	
77	425	5.88	57.0	0.588	52.1	
87	425	6.10	7.53	0.570	52.8	
80	427	6.20	6.10	0.487	22.3	
81	350	6.23	1.83	1.80	5.61	
78	354	6.30	50.8	0.625	6.21	
82	357	6.35	67.1	0.612	8.83	
86	358	6.52	7.08	0.588	6.37	
80	358	6.52	6.60	0.6400	8.0	
81	355	6.61	6.30	0.6475	20.5	
83	296	6.13	6.2	0.681	1.08	
79	298	6.49	47.0	0.663	0.92	
85	297	5.90	66.0	0.502	1.05	
88	300	6.27	7.18	0.6600	0.53	
4(b). Vinyl Iodide in Nitrogen.						
91	506	5.20	50.8	1.27	0.073	
92	508	5.44	35.2	0.545	0.21	
5(a) Benzyl Iodide (Carrier-Gas : Hydrogen).						
61	492	6.28	1.22	0.242	2.53	
67	493	6.01	1.24	0.245	2.40	
60	492	5.80	1.22	0.254	2.34	
64	492	6.20	1.50	0.023	4.65	
66	433	5.49	3.82	2.11	10.1	
62	429	6.13	1.18	0.206	37.8	
63	429	6.57	1.389	0.240	30.3	
65	430	6.22	1.32	0.0224	46.9	
5(b). Benzyl Iodide (Carrier-Gas : Nitrogen).						
68	495	5.68	1.73	0.591	70.4	
69	494	6.73	1.38	0.0439	322.0	
70	430	5.01	1.70	0.040	18.5	
71	431	5.01	1.56	0.0312	26.8	
73†	431	5.85	1.56	0.035	10.6	
5(c). Phenyl Iodide in Hydrogen.						
49*	511	7.51	30.8	0.224	0.89	
50†	509	6.53	30.2	0.577	1.76	
* 11g vapour present. † Carrier-gas : NO.						
6(a). Acetyl Iodide in Nitrogen.						
73	494	6.18	84.8	0.517	3.54	
74	392	5.01	61.7	0.503	1.84	
75	364	6.28	47.3	0.597	1.41	
6(b). Benzoyl Iodide in Nitrogen.						
98	430	5.37	3.40	0.619	9.87	
103	430	6.76	5.00	0.600	10.4	
102	430	5.59	4.04	0.0468	36.4	
104	431	5.75	5.36	0.0468	36.4	
99	390	6.93	3.75	0.630	36.3	
100	390	5.99	3.64	1.26	2.33	

TABLE I.—Continued.

Exp. No.	Temp. °C.	Total Prc. % mm.	Iodide Prc. % $\times 10^{-3}$	Contact Time. sec.	k_I $(\text{lit.} \times 10^{-3})$	k_{HI} $(\text{lit.} \times 10^{-3})$
7(a). Acetonyl Iodide in Nitrogen.						
31*	493	7.13	87.2	2.68	5.98	
35*	491	7.70	42.6	0.500	1.13	
36*	491	7.23	33.5	0.640	9.70	
37	151	6.71	25.1	0.530	3.18	
93	420	6.48	37.3	0.584	2.52	
97	382	6.37	33.3	0.506	0.90	
96	383	5.16	23.8	0.73	0.45	

* Hg vapour present.

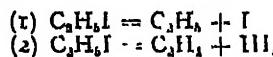
7(b). Methyl Iodide in Nitrogen.

130	491	6.42	3.32	0.615	2.33
131	495	4.97	3.10	0.585	5.17
132	494	5.50	2.76	0.592	2.70
133	491	7.00	3.50	1.51	7.80
134	493	6.88	12.3	1.03	3.05

observable at all—for ethyl iodide in nitrogen, to which Table I (2) refers. We would not venture to ascribe any of the variations of k_I here shown (apart from Exps. 32-33) to the corresponding changes in the reaction variables. A distinct rise to about twofold values of k_I is caused by the admixture of NO in Exps. 32-33.

In Table I (2) there also appear values for k_{HI} expressing the rate of HI-formation which was not tested previously. This reaction proceeds at a rate perceptibly equal to that of the formation of iodine, except in Exps. 32-33 where it shows itself unaffected by the admixture of NO.

Taken by themselves the experiments in nitrogen would form a sufficient proof for the presence of a pair of truly monomolecular reactions



the first of which leads to the formation of I₂. The process 2I → I₂ may be assumed to occur with less than 100% yield owing to losses likely to be caused by the back reaction C₂H₅I₂ + I → C₂H₅I. It may be thought that the undiminished primary decomposition (1) is observed in Exps. 32-33 where the NO present removes the free radicals.

This picture is consistent with all the later experience on pyrolysis of iodides both in the presence of nitrogen and hydrogen, but it is not easy to reconcile with some of the results of Table I (1). Even admitting the possibility of a reaction sequence on the lines C₂H₅I + HI → C₂H₅I₂ + H₂ + C₂H₄I → C₂H₅I₂ + I, the yield in Exps. 9-10 still appears to be inexplicably high, especially taking into account that further reduction in contact time and increase in pressure seems to increase k_I even more. Such difficulties do not recur throughout the whole of the investigation recorded in this and the following paper. In view of this fact (and considering also that the experiments in Table I (1) were the very first results obtained by the new technique utilised throughout the rest of the investigation) we did not think it right to suspend indefinitely the detailed evaluation of all the material hitherto collected, but preferred rather to disregard for the time being the difficulties which the interpretation of Table I (1) presents and to lay all the stress on the mass of later experiments from Table I (2) onwards.

Measurements on *n*-propyl iodide and *n*-butyl iodide, are recorded in Table I (3). Exps. 112-109-108-113 show that neither the variation of the iodide pressure nor the very large changes in contact time have any definite effect on k_I . The formation of HI continues to occur as in ethyl iodide at

about the same rate as that of I_2 . The admixture of NO in Exp. 115 had no effect; nor did the replacement of N_2 by H_2 in 114 produce any change. We will return to the measurements at lower temperature (110 and 111) later.

For *n*-butyl iodide there is again a wide variation of contact times in Exps. 121-125-118-112 without any definite change in k_t . HI-formation is somewhat larger in proportion to I_2 -formation and is less reproducible.

Comparison of ethyl iodide in nitrogen with *n*-propyl and *n*-butyl iodide shows a definite increase in the rate of pyrolysis both in the production of I_2 and of III. For ethyl : *n*-propyl : *n*-butyl k_t at 492° = 1 : 4.3 : 7.4 k_{III} at 492° 1 : 5.0 : 11.6. Extrapolating the data of Exp. 111 to 440° by use of temperature coefficient evaluated from Table I (r) we obtain for the ratio of k_t at 440° 1 : 4.7 : 7.0.

Table I (4) (a) shows that allyl iodide decomposes much more readily than any of those previously described. At 494 decomposition was almost 60 %, so that in order to obtain more moderate decomposition lower temperatures had to be chosen. Exps. 77-78 show the absence of any effect of iodide-pressure on the rate. The comparison of these results with Exp. 80 reveals a fourfold increase of k_t caused by a twelvefold reduction of the contact time. Exps. 84, 78, 82 and 86, carried out at the lower temperature of about 356° again show k_t as independent of the iodide pressure. Comparing Exp. 84 with Exps. 78, 82 and 86, and the latter with Exps. 80 and 81, we see also that the rise of k_t with diminishing contact time has become less marked if not altogether negligible. With a further lowering of the temperature to about 298° (Exps. 83, 79, 85, 88) the dependence of k_t on contact time becomes quite imperceptible. Thus with decreasing temperature the kinetics of the reaction appear to conform increasingly well to the monomolecular scheme. Extrapolating the rate of pyrolysis of *n*-propyl iodide down to 298°, the ratio of k_t for *n*-propyl : allyl can be calculated at about 1 : 14000.

The striking increase in the rate of pyrolysis observed in passing from the saturated iodides to allyl iodide is contrasted by a considerable variation in the opposite direction in the case of vinyl iodide—Table I (4) (b). At the standard temperature of 493° no decomposition could be observed. The highest accessible temperatures (506°-508°) had to be applied in order to obtain a measurable result. While no great accuracy can be claimed in these circumstances, Exps. 91-92 leave no doubt that k_t is considerably reduced here as compared e.g. with ethyl iodide—the rates for both substances being extrapolated to the same temperature, 507°. For the ratio ethyl : vinyl we calculate k_t about 16 : 1.

Next we come—in Table I (5)—to benzyl iodide and phenyl iodide. Benzyl iodide was measured both in hydrogen and in nitrogen at two temperatures; in Exp. 73 NO was used as carrier gas. At 493° there is both for H₂ and N₂ carrier gas a deviation from the monomolecular form in the sense of higher k_t values being obtained at shorter contact times; but again this behaviour is much reduced by lowering the temperature, as the experiments at 430°-431° indicate. The presence of hydrogen increased the production of I_2 almost twofold both at 493° and 431°; while NO shows no effect at all. Comparison of the rate of pyrolysis with that of ethyliodide at 431° (taking both iodides in nitrogen) yields for ethyl : benzyl k_t about 1 : 4800.

In the experiments with phenyl iodide there was again no observable decomposition at the standard temperature of 493°; but we obtained pyrolysis at 510°. We may estimate for phenyl : ethyl k_t about 1 : 3.

Acid iodides were tested by the examples of acetyl iodide and benzoyl iodide. The sensitivity to light of the former compound caused traces of iodine to be formed even without pyrolysis. The observations in Table I (6) can justify nothing more than the claim that at the temperature of 493° k_t for acetyl iodide is around 2 to 3 × 10⁻³. Benzoyl iodide is seen to be far more readily decomposed than acetyl iodide. However, at 430

there occurs an almost fourfold increase of k_1 when contact time is reduced twelvefold, and a similar feature is present at 390°; which makes k_1 as a monomolecular reaction constant very uncertain. Yet we may note that while the decomposition of acetyl iodide is about twice as fast as that of ethyl iodide, there is about a 2000-fold increase of the rate from ethyl to benzoyl iodide—comparing these two substances at 390° and taking the shortest measured time of contact from Table I (6) for benzoyl iodide.

Finally we add some observations on acetonyl iodide and methyl iodide. We had considerable difficulty with the former substance on account of the decomposition which it undergoes by light and even on standing. Yet Table I (7) may reasonably indicate the position of this compound among other iodides. It lies between benzoyl and *n*-butyl, so that *n*-butyl < acetonyl < benzoyl; roughly in the ratio 1 : 4 : 70. While methyl iodide gave no reproducible results, its pyrolysis proved very distinctly slower than that of ethyl iodide. The mean rate constant $4.2 \times 10^{-8} \text{ sec.}^{-1}$ is about 3 times less than that of ethyl iodide.

We may use the observations listed above to derive in some cases the temperature coefficients of the rate of pyrolysis and hence the activation energy of the reaction. For *n*-propyl iodide and *n*-butyl iodide we have sufficiently reliable data for two temperatures from which we calculate: for *n*-propyl $Q = 52$ kcal. and for *n*-butyl $Q = 53$ kcal. This lends support to the value of similar magnitude, $Q = 55$ kcal., obtained from the otherwise less reliable Exps. 3, 4, and 6, 7, 8 for ethyl iodide.

The measurements for allyl-, benzyl-, and benzoyl iodide and acetonyl iodide all show at higher temperatures a variation of k_1 with contact time which makes the calculation of an activation energy uncertain. Since in view of the conditions of our experiments we can exclude errors which would increase the rate of decomposition, we consider the higher values which are observed at the shorter contact times as nearer to the truth and have selected the data for calculation in accordance with this view. When we combine for allyl iodide the average of the experiments made at 298° with (a) Exp. 81 (b) Exp. 89 (c) Exp. 80 we obtain for Q (a) 39 (b) 27.5 (c) 34.0. For benzoyl iodide we may rationally choose (a) Exps. 64 and 65, and (b) Exps. 69 and 71 as representing the highest values of k_1 for both temperatures and carrier gases. We obtain for Q (a) 47.5, and (b) 48.5. For benzoyl iodide the most rational seems to be, on similar grounds, to choose Exp. 99 combined with the average of 102 and 104 which leads to $Q = 53$; alternatively we obtain from Exp. 99 and the mean of 98 and 103 $Q = 24$. For acetonyl iodide Exps. 36 and 37 yield $Q = 27$.

Before discussing these values, we may try to derive activation energies by the alternative method of using the equation for the rate of monomolecular decomposition $k = v e^{Q^*/RT}$ where v is usually about 10^{12} . The difficulty is here that we do not know for certain what fraction of the primarily formed iodine is lost by recombination either while the gas is at the reaction temperature or during the subsequent phase of cooling. Tentatively assuming that recombination is negligible, at least at the lowest temperatures and pressures when conformity to the monomolecular form was closer—and limiting ourselves for the sake of uniformity to the results in nitrogen—we obtain from $k_1 = 10^{12} e^{-Q^*/RT}$ the series of Q^* values listed in Table II.

Now if the yields of iodine were much less than the assumed value of unity, the energies Q^* would be considerably higher than the true activation energies; a yield of 0.1 for example would cause Q^* to be too large by 3 kcal. For a number of compounds such an assumption seems unacceptable. For *n*-propyl iodide and *n*-butyl iodide the activation energies calculated from $k_1 = 10^{12} e^{-Q^*/RT}$ at the temperature of 493° are 49.9 and 48.9 kcal. respectively, which values scarcely differ from Q^* calculated for the lower temperature and listed in Table II. This fact is reflected once more in the satisfactory correspondence between the energies Q^* and the activation energies $Q = 52$ and $Q = 53$ calculated from the

TABLE II

Iodide.	Q^* kcal.	$k_1(130^\circ) \times 10^5$ sec. ⁻¹	$T(1\% \text{ per sec.}) \text{ in } ^\circ\text{C.}$
Methyl	(34)	14	516
Ethyl	52.2	50	480
<i>n</i> -Propyl	50.0	250	457
<i>n</i> -Butyl	49.0	500	442
<i>iso</i> -Propyl	46.1	1000	398
tert Butyl	45.1	9000	385
Allyl	39.0	130000	297
Vinyl	55.0	10 ³	520
Benzyl	43.7	23000	300
Phenyl	54.0	14	516
Acetyl	(50.7)	160	445
Benzoyl	43.9	18000	360
Acetonyl	45.0	9000	385

temperature coefficient derived from the same data. It leaves no room for the assumption that the true activation energy is noticeably less than Q^* .

We could try to get nearer to the truth about the reduction of the yield due to the back reaction by using our observations in the presence of NO. Its ineffectiveness in case of *n*-propyl iodide might be taken to confirm the assumption that the yield of iodine is unreduced in this case; while from Exps. 29, 30 and 32, 33 on ethyl iodide it might be suggested that for this substance the yield is reduced to about 0.5. This would mean that Q^* for ethyl iodide exceeds the activation energy by 1 kcal. These considerations, however, would strain the present evidence too far—particularly in view of the uncertainty of the value of the factor ν and of its possible variations from one substance to another. Comparing the value $Q^* = 44$ for benzyl iodide with the Q -values from the temperature coefficient ((a) 47.5, and (b) 48.5) there again seems little possibility for the activation energy to be markedly less than Q^* .

In the cases of allyl and benzoyl iodide the Q values are too scattered to justify comparisons with Q^* ; but there is nothing to suggest that the behaviour of these compounds differs much from that of the others already discussed. We have assumed this behaviour to hold also for vinyl and phenyl iodide for the purpose of constructing Table II for the extrapolation of the k_1 values for vinyl and phenyl iodide to 430° by use of a temperature coefficient derived from Q^* .

The mean value of 54 kcal. given from Q^* of methyl iodide results from the experiments listed in Table I (7) from which values ranging from 53 to 55 kcal. were obtained.

Comparisons between the values of Q^* and Q can also be used to examine the possibility of the observed rate, as postulated by the theory of monomolecular reactions, falling short of the limiting rate for high pressures. The kind of argument we have just used applies here with even greater force, since if the rate were limited by energy transfer we should have to postulate that the correct activation energy is less than Q^* and higher than Q . We see that, at least for the two compounds *n*-propyl and *n*-butyl iodide there is no room for such an assumption, and that it is also contrary to the less reliable data for ethyl, allyl, benzyl and benzoyl iodides.

We conclude that though some inaccuracy of our results on account of the recombination of R + I and of the possible insufficiency of energy transfer cannot be excluded, these influences cannot be of sufficient magnitude to account to any considerable extent for the range of variations in the rate of pyrolysis which we observed. We attribute therefore this range—which is represented in Table II by the $k_1(430^\circ)$ values calculated for the temperature of 430° (at which the largest number of common observations were made) as well as by the calculated temperatures $T(1\% \text{ per sec.})$ at which k_1 would have the common value of 1 % per second—to the

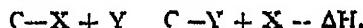
variation in the primary rates of decomposition of the C—I bond in the different compounds.

Bond Energies and "Bond Energy Terms".

Our use of the equation $k_t \propto e^{-Q^*/RT}$ implies that Q^* is the energy required for breaking the C—I bond. We will consider, therefore, that the Q^* in Table III represent the Bond Energies for the various iodides in question; the C—I Bond Energy being defined as the dissociation energy of the molecule into a free radical and an iodine atom.

In this identification of the activation energy Q^* with the Bond Energy (D) we apply the usual conception of a chemical bond derived from the theory of diatomic molecules which postulates an energy curve monotonously rising from the normal state to complete dissociation. We note, however, that for hexaphenylethane Q^* has been observed to be 8 kcal. in excess of D for the ethane linkage. But this case may be considered as exceptional in various respects. For one thing there is likely to be present (as a Fisher model of hexaphenylethane clearly demonstrates) a very considerable steric hindrance opposing the formation of the ethane linkage, and this may cause considerable repulsion to occur before the valence force begins to become effective. In any case we do not feel that the deviation from $Q^* = D$ for hexaphenylethane necessitates any serious reservation in the identification of these two magnitudes for bonds of a more usual character.

Turning now to the theorem first postulated by Fajans⁴ and elaborated much further by Sidgwick⁵ and Pauling⁶ according to which the heat of formation of organic compounds from free atoms can be represented as the sum of constant contributions characteristic of each chemical link, we note first that the validity of this theorem constitutes no evidence for the existence of a constant heat of formation of the bonds covered by its scope. Take two kinds of bonds formed, say, by carbon with the two different atoms X and Y. Whatever the variation may be in the energies of the C—X and C—Y bonds with the position of the C-atom, no deviation from the additivity rule would result, so long as the variations are equal for both kinds of bonds; the additivity rule merely expresses the constancy of the substitution heat — ΔH_s in the reaction

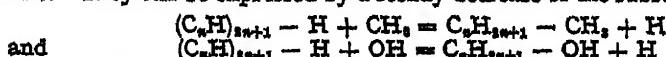


independently of the position of C.

It seems logical to express this state of affairs by designating the constant contribution attributed to one chemical link the *Bond Energy Term* of that link as distinct from the *Bond Energy* (D) as defined, e.g., above for the C—I bond.

The evaluation of Bond Energy Terms starts from a compound containing only one kind of bond (e.g. CII_4 , CCl_4) and proceeds by dividing up the heat of formation of the molecule by the number of bonds present. The *Bond Energies* of C—H, C—Cl, etc., in CH_4 , CCl_4 , etc., on the other hand, are defined for the breaking of one bond only, and may thus differ considerably from the corresponding Bond Energy Term.

The investigations of Rossini⁷ on the heats of combustion of the aliphatic hydrocarbons and of primary alcohols derived from these have proved the existence of some remarkable deviations from the additivity rule. They can be expressed by a steady decrease of the substitution heats



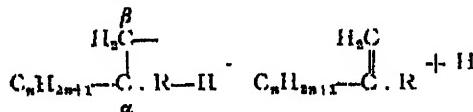
⁴ Fajans, *Ber.*, 1920, 53, 643; 1922, 55, 2826.

⁵ Sidgwick, *The Covalent Link in Chemistry*, Cornell, 1933.

⁶ Pauling, *The Nature of the Chemical Bond*, Cornell, 1939.

⁷ Rossini, *Bull. Bur. Standards J. Research*, 1934, 13, 29, 189; Knowlton and Rossini, *ibid.*, 1939, 22, 115.

with n increasing from 1 onwards, the main change being between CH_3 and C_2H_5 , and approximate constancy being reached after $n = 5$. Other deviations from the additivity rule were discovered by Kistiakowsky⁸ in the case of the heats (1) of hydrogenation, and (2) of bromination of olefines. These can be expressed again, as Baughan and Polanyi⁹ have suggested, as a variation of the substitution heats of a C-H link with varying position of the carbon. The observed changes in the heat of hydrogenation are expressed in the reaction



for the same α carbon position as explored by hydrogenation.

We thus have evidence that the differences between bond energies vary in simple hydrocarbons and in substituted hydrocarbons: but so far this leaves us in the dark as to the variations of the individual values. Definite indications—if only of an approximate nature—of wide variations in bond energies were first postulated by Ogg and Polanyi¹⁰ from the variations in the rates of reaction between organic halides and sodium vapour observed by Hartel and Polanyi.¹¹ More recently H. S. Taylor and Smith¹² derived similar conclusions from the marked variations in the rate of reaction of methyl radicals with hydrocarbons. A fall in the bond energy of C-H was quite recently confirmed and quantitatively fixed by more direct methods. D. P. Stevenson¹³ has given the values as $D(\text{CH}_3-\text{H}) = 101$ and $D(\text{C}_2\text{H}_5-\text{H}) = 96$ while independently and by different methods Anderson, Kistiakowsky and van Arstdalen¹⁴ obtain $D(\text{CH}_3-\text{H}) = 102$ and $D(\text{C}_2\text{H}_5-\text{H}) = 98$ kcal.

Bond Energies and Activation Energies.

It was one of the main purposes of this investigation to test the theoretical conclusion that the observed gradation in the rate of the reaction between Na and organic halides is due to a corresponding gradation in the energy of the halide bond. This postulate is illustrated by Fig. 2, taken from the above cited paper of Evans and Polanyi,¹⁰ which reflects the simplification achieved by neglect of repulsion between the Na and Cl atoms in (the initial half of) the transition state. The variation ΔQ in the activation energies is connected here with the variation ΔH of the heat of reaction by the proportionality relation

$$\Delta Q = -\alpha \Delta H$$

$$0 < \alpha < 1$$

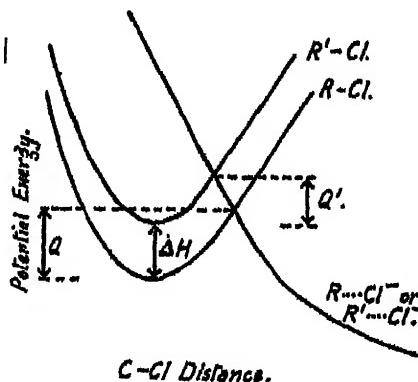


FIG. 2. $Q - Q' = \Delta Q = -\alpha \Delta H$.

⁸ Kistiakowsky et alii, *J.A.C.S.*, 1936, 58, 137; 1937, 59, 831; 1938, 60, 440
2764. ⁹ Baughan and Polanyi, *Nature*, 1940, 146, 685.

¹⁰ Ogg and Polanyi, *Trans. Faraday Soc.*, 1935, 31, 1375. Further developed by Evans and Polanyi, *ibid.*, 1938, 34, 11. Calculations based on this theory were carried out for the Na + Methyl halide reaction by Evans and Warhurst, *ibid.*, 1939, 35, 593.

¹¹ Hartel and Polanyi, *Z. physik. Chem. B*, 1930, 11, 97; 1932, 19, 139.

¹² H. S. Taylor and Smith, *J. Chem. Physics*, 1939, 7, 390; 1940, 8, 543.

¹³ Anderson, Kistiakowsky and Arstdalen, *ibid.*, 1942, 10, 305.

where the value of α depends on the relative inclinations of the attraction curve R—Cl and the repulsion curve R . . . Cl⁻ at the point of mutual crossing. Since the latter curve is bound to be much steeper than the former, it follows that α is always smaller than $\frac{1}{2}$.

This derivation implies that changes in the bond energy will be reflected, in the region of the "crossings" and below that, by vertical parallel displacements of the potential curve. This would be strictly true if the variations of bond energy were due entirely to variations in the resonance energy of the free radical, which would leave the potential curve unaffected in regions near the hollow of the curve. Actually there is always a certain amount of resonance present in the undissociated bond and in certain cases, like the vinyl halides, this resonance—and its absence in the free radical—may be entirely responsible for the variation in bond strength. In this case, and in general whenever substitution affects resonance in the undissociated state, this influence must vary to some extent with nuclear separation and a change in the shape of the energy curve in the region of the equilibrium distance will follow.

It seems, however, scarcely worth while to attempt the very uncertain evaluation of these deviations from the simple scheme of Fig. 2, since they are not likely to affect the first approximation attempted here. We have therefore proceeded to evaluate the scheme indicated by Fig. 2, for which purpose we calculated the curves shown in Fig. 3.

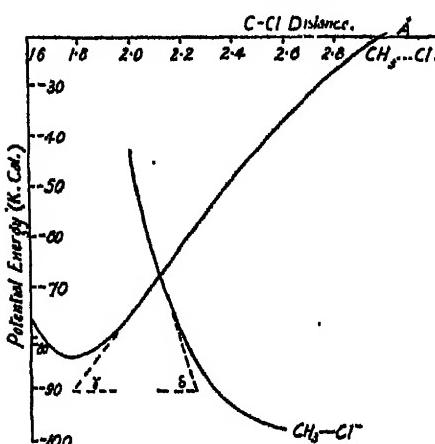


FIG. 3.

These relate to the reaction Na + ClCH₃ = NaCl + CH₃. The chlorine compounds are taken here instead of the iodine compounds because the gradation of the rates of reaction with Na-vapour is much more widely spaced for the chlorides than for the iodides, and hence it is desirable to transfer the argument to the former. This can be done by using the gradation of the C—I bond strength as representing also the gradation of the C—Cl bond strength.

The implied assumption of a constant substitution heat of C—I by Cl is sufficiently well supported to justify this move—which certainly can cause no serious error in our conclusions.

The curve in Fig. 3 represents the C—Cl bond, according to a Morse function with $D = 83.5$, $r_0 = 1.76\text{\AA}$, $\omega_0 = 710 \text{ cm}^{-1}$ and hence $a = 1.66 \times 10^8$. The value of D corresponds in view of the known thermochemical data to $D = 54$ for ClI₂I. The repulsion curve between Cl⁻ and CH₃ was calculated in accordance with M. G. Evans and E. Warhurst¹⁰ by the equation

$$E = -\frac{ae^2}{r^4} + br^{-6},$$

using $\alpha = 2.2 \times 10^{-24}$ c.c., and (for the determination of b) $r_0 = 3.01\text{\AA}$.* The activation energy as indicated by the crossing point in Fig. 3 would

* This value is the sum of the CH₃ radius 1.40\AA as used by Evans and Warhurst¹⁰ and the Cl⁻ radius of 1.6\AA estimated from electron-diffraction data of gaseous alkyl-halides by Maxwell, Hendricks and Mosley, *Physic. Rev.*, 1937, 52, 968 (see Baughan and Polanyi, *Trans. Faraday Soc.*, 1941, 37, 648).

be 16.0 kcal., which is somewhat higher than the experimental value of about 10 kcal. The difference of 6 kcal. may be accounted for by transition state resonance, which in the theory represented by Fig. 2 is supposed not to vary with the nature of R and to have therefore no influence on changes of E with varying R. Accordingly the coefficient α in $\Delta E = -\alpha \Delta H$ remains represented by the ratio of the inclinations of the two curves at the "crossing point," and can be estimated from Fig. 3 at the value 0.27.¹⁴

An attempt to plot the observed activation energies of the Na + CIR reaction as functions of the corresponding C—I bond energies (as representing the gradation of the C—I bond energies) leads to Fig. 4. Here are included the two compounds iso-propyl iodide and *t*-butyl iodide for which the bond energies are derived in the following paper and the four compounds acetyl, acetonyl, benzoyl and benzyl iodides¹⁵—for which the activation energies are 5.0, 2.0, ~0 and 0.9 respectively—are left away because the values fall into an altogether different region.

The compounds shown in the figure are allyl, *t*-butyl, iso-propyl, *n*-butyl, *n*-propyl, ethyl, phenyl, vinyl iodides. They comprise all the pure hydrocarbons measured in this paper, and the next one for which the ratio of the Na reaction is known. For this group the evidence in the figure is consistent with a linear relationship of the form $\Delta E = -\alpha \Delta H$ where $\alpha = 0.28 \pm 0.015$ corresponds to the minimum of squared deviations. This value of α seems remarkably close to the value $\alpha = 0.27$ derived theoretically from Fig. 3, but even without relying in any way on this close correspondence, it would seem that strong evidence has been found here for the mechanism of the reactions of alkali metals with organic halides as postulated by Ogg and Polanyi. The evidence will also strengthen the case for considering the kind of linear relationship of which Fig. 4 is a particular instance as fundamentally determined by the relationship between reaction heat and activation energy in the sense suggested by Evans and Polanyi.¹⁶

It may be objected that the compounds in Fig. 4 represent a selection which is not justified by the theory. This is true of the original form of the theory as represented by Fig. 2; but a note of Evans and Polanyi¹⁶ has recently pointed out theoretical and experimental reasons for extending this theory by taking into account changes in transition state resonance due to variations of R. In a reaction $\text{Na} + \text{XRX} \rightleftharpoons \text{NaX} + \text{RX}$ there are three structures, instead of the usual two, resonating in the transition state:

¹⁴ If $\tan \gamma$ and $\tan \delta$ be the inclinations at the crossing point $\frac{x}{\alpha} = \frac{\tan \delta}{\tan \gamma} + 1$.

¹⁵ From unpublished work in these laboratories.

¹⁶ Evans and Polanyi, *Trans. Faraday Soc.*, 1936, 32, 1333.

¹⁷ Evans and Polanyi, *Nature*, 1941, 148, 436.

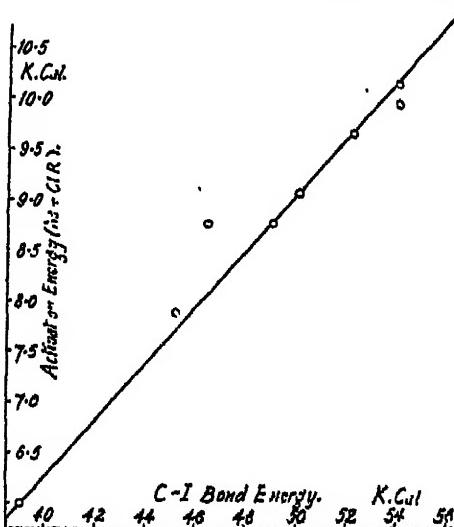
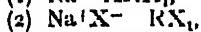


FIG. 4.



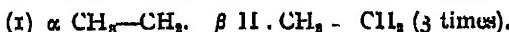
as well as

The effect of the negative substituent X is thus to cause an extra depression of the activation energy below the "crossing point," and thus to accelerate the reaction beyond the rate which it would have in view of the bond-energy if the relationship $\Delta E = \alpha \Delta H$ held. This effect of negative substituents may well explain all the deviations from the linear relationship established in Fig. 4. We note in particular that all deviations represent *faster* rates than given by the straight line; that all the deviating compounds (except benzyl iodide) contain substituents, known to possess negative character, and that conversely all compounds containing negative substituents show marked deviations from the straight line relationship in the expected direction. This statement includes the experimental material both of this and the next paper. The fact that benzyl falls into the negatively substituted group of radicals is surprising, and will require explanation; but we do not feel that this fact goes far to invalidate the scheme from which it forms an apparent exception.

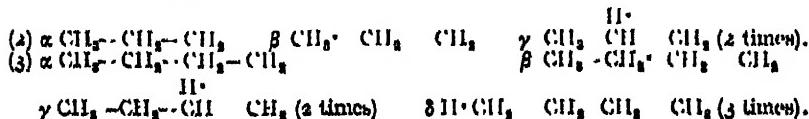
Bond Energy and Resonance.

We follow here the lead of the theory first proposed as an explanation of the existence of free radicals by Hückel¹⁷ and by Pauling,¹⁸ according to which variations in bond energy are to be attributed to changes in the difference between the resonance energies of a molecule held together by the bond in question and the two halves of the molecule resulting from the splitting of the bond. With few exceptions the changes in bond energies which we have observed can be accounted for in this sense by some previously known form of resonance.

A fall in Bond Energy from CH_3-I to $\text{CH}_2\text{CH}_2-\text{I}$ was first postulated by Wheland¹⁹ on account of an additional resonance due to the substitution of one H atom by a CH_2 group. This can be written:



We take this to be the explanation for the observed fall of D from methyl to ethyl iodide, and we would extend the scheme to include the further fall of D observed for *n*-propyl and *n*-butyl iodide, as follows:



It seems likely that the β form postulated for the *n*-propyl radical adds more to the resonance energy than the corresponding β form of ethyl, since the energy of the former is lower by the difference between a C—I and a C—C bond. In case of resonance (3) we have the number of resonating forms increasing from 4 to 7 which may well increase the resonance of *n*-butyl over that of *n*-propyl. It seems reasonable to assume that the magnitude of this kind of resonance increases further on these lines with further increasing chain length. This seems indicated by the fact that in the case of *n*-aliphatic hydrocarbons and alcohols Rossini found variations in the substitution energy with increasing normal chain length even as far as the fifth carbon atom.

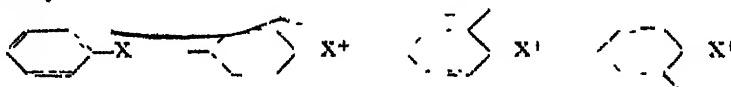
¹⁷ E. Hückel, *Z. Physik*, 1933, 83, 632.

¹⁸ Pauling and Wheland, *J. Chem. Physics*, 1933, 1, 362.

¹⁹ Wheland, *ibid.*, 1934, 2, 474.

To avoid repeating the argument on this point later we include here a reference to the *iso*-propyl and *t*-butyl radicals which we have already briefly discussed in connection with Fig. 4. It has been pointed out by Wheland that the number of resonating forms increases in the series ethyl, *iso*-propyl, *t*-butyl from three to six and to nine. This should cause a steady increase in resonance energy and may explain the observed steady fall in the bond energy.

Our results for allyl and benzyl iodides can be compared with the predictions of Pauling¹⁸ and of Hückel,¹⁹ concerning the resonance between a free valence and a double bond in β -position to it. The resonance energies were calculated by Coulson²⁰ and by Pauling and Wheland²¹ at 15.4 kcal. for allyl and 15 kcal. for benzyl radicals; while we found a reduction in the corresponding C—I bond energy of 15 kcal. and 11 kcal. respectively. To complete the comparison we should, however, yet consider the ionic resonance in the undissociated bond, to which we refer in the last chapter. Our values for vinyl and phenyl iodides confirm the existence of the following kind of resonance assumed by Pauling²¹ to account for the shortening of the C—Halogen bond-length and the reduction in the dipole moments of the vinyl and phenyl halides when compared with the methyl halides:



This degeneracy should cause the C—I bond to be strengthened as compared with the CH_3-I bond, as we, in fact, find it to be for vinyl iodide. In the case of phenyl iodide there is a possible offsetting effect due to the following degeneracy of the phenyl radical:



M. G. Evans and E. Warhurst¹⁰ suggest that the magnitude of this resonance energy is of the order of 10 kcal., but our experiments indicate a much lower value.

In spite of the inaccuracy of our value for acetyl iodide we think that we have established that the C—I bond energy in this compound is not greater but rather less than that in ethyl iodide, which raises some important points. In view of its α double bond, acetyl iodide should show the same resonance as vinyl iodide,

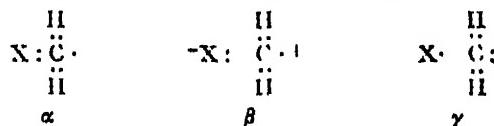


and hence its C—I bond should be much stronger than that of ethyl iodide. The fact that this is not observed suggests that the effect is offset by some other factor. Observations on dichloro- and dibromoiodo methane to be described in the following paper indicate that the presence of halogen substituents lowers the C—I bond energy in these compounds. If this were due to the electron-attractive nature of the halogen atoms, a similar effect could be postulated for the O-atom in acetyl iodide, and this would offer the required explanation.

¹⁸ Coulson, *Proc. Roy. Soc. A*, 1938, 164, 383.

¹⁹ Brockway, Beach and Pauling, *J.A.C.S.*, 1935, 57, 2693; Brockway and Palmer, *ibid.*, 1937, 59, 2181.

If X is a negative substituent, the following resonance may arise in the free radical and contribute to its stability as follows



which can also be written by the use of a three-electron bond (using the symbol of three dots suggested by Pauling for this kind of link) :



The same kind of resonance will be much less marked in the absence of a lone electron, i.e., when the radical forms part of a molecule. The difference reduces the energy of the bond. We may assume that the effect will depend on the stability of the form β in the above resonance formula, i.e., on the negativity manifested by the substituent X, and we may expect therefore that another strongly negative substituent like oxygen will act in the same sense and weaken the strength of an associated bond C—I. This would explain that the bond energy in acetyl iodide is weakened instead of strengthened—in comparison to CH_3I .

In benzoyl iodide the situation is even more complex. In addition to the two opposing resonance effects manifested in CH_3COI , we may expect to find here also a weakening of the bond due to resonance with a β unsaturation. If the effects corresponding to the acetyl-structure and to β conjugation were additive, the bond energy should fall somewhat short of that observed in benzyl iodide; our results indicate that, in fact, it about coincides with the latter.

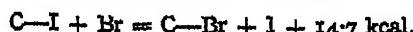
In acetonyl iodide we might expect to see the appearance of resonance due to a β conjugated double bond. To this will be added any effects that β substitution by a negative particle may exercise. Evidence that substitution by a halogen atom in β position does weaken a bond will be given in the next paper. We may explain this by the resonance :



The oxygen atom in β -position—as in acetonyl iodide—may be expected to have an influence similar to that of X. The reduction of bond energy by about 10 kcal. observed for acetonyl iodide is thus seen to represent the sum of two types of resonance.

Bond Energies and Substitution Heats.

Substitution heats are differences of bond energies. Following Baughan and Polanyi, we have set out in Table III a system of substitution heats, all of which were related to the C—H link as the initial state. Once the absolute values for any one kind of bonds become available, all the bond energies represented in it can forthwith be calculated. While the C—I bonds which we investigated here do not form part of the system as it stands, yet the results obtained for these bonds can be used to throw light on the gradation of the C—Br bonds which do form part of it. This was done by Baughan and Polanyi by using the assumption (for which they adduce evidence) of a constant substitution heat of the reaction



We have thought it useful to reproduce the resulting table of bond energies in the present context, with such revisions as more recent observations and

TABLE III. SUBSTITUTION HEATS (FROM BAUGHAN AND POLANYI).

R.H.	X-CH ₃	X-Br	X-OH	X-β
CH ₃ II	15.4	(33.9)	16.0	-
C ₂ H ₅ II	13.0	30.5	10.2	68.0
n-C ₃ H ₇ II	12.7	30.1	8.8	67.5
n-C ₄ H ₉ II*	12.7	30.0	8.2	-
iso-C ₃ H ₇ II	10.8	27.9	4.5	66.0
tert-C ₄ H ₉ II	10.0	25.0	0.0	64.0

TABLE IV. BOND ENERGIES OF BAUGHAN AND POLANYI (REVISED).

(To the nearest half calorie.)

R.	C-I.	C-Br	C-II.	C-CH ₃	C-OH	α-β
CH ₃ I	54.0	68.5	102.5	87.0	86.5	-
C ₂ H ₅ I	52.0	67.0	97.5	85.0	87.0	57.5
n-C ₃ H ₇ I	50.0	64.5	95.0	82.0	86.0	-
n-C ₄ H ₉ I*	49.0	63.5	91.0	81.0	85.5	-
iso-C ₃ H ₇ I	46.5	61.0	80.0	78.0	84.5	52.5
tert-C ₄ H ₉ I	45.0	60.0	80.0	75.5	85.0	54.0

α-β signifies the "second half" of a double bond.

* n-butyl was not included in the original table of Baughan and Polanyi. The figures given here for substitution heats are calculated from the same sources

the more detailed analysis of the experiments allowed us now to make. The main difference between our table and the previously published one comes from the fact that we refrained from smoothing the observed values because we felt doubtful whether this rather considerable correction is sufficiently supported on theoretical grounds.

The table brings out the fact that our estimate of the bond energies is consistent with the previously suggested values for the C-H bond energy in methane, which various authors have put at 100-108 kcal., and is well in excess of the average bond energy of CH₃ calculated at 87 kcal. by Sidgwick and Pauling.* This point has gained considerable precision by the more recent publications already mentioned above, by D. P. Stevenson¹² and Anderson, Kistiakowsky and Artsalalen,¹³ who—by entirely different methods—arrive at values for the CH₃-H bond energy of 101 and 102 ± 1 kcal. respectively, which come quite close to the figure suggested by us. The force of this argument seems to decide that the older determinations of the C-I bond energy from kinetic experiments¹ which gave a value of 44 kcal. for CH₃-I cannot be maintained.

The unequal gradation of bond energies in the alkyl bonds was explained by Baughan, Evans and Polanyi,¹⁴ by the presence of ionic resonance in the undissociated bond which tends to offset the resonance of the free radicals. Ionic resonance is small in the C-H bond, and we therefore observe here almost the whole resonance of the free radical as a reduction of the bond energy. Our previous comparison of the resonance of the free radical with the reduction in the strength of the corresponding bond energies—for example in the case of allyl and benzyl—is now seen to be incomplete; owing to ionic resonance we should expect the reduction of the C-I bond energy to be generally somewhat smaller than the resonance energy of the free radical.

* Baughan, Evans and Polanyi, *Trans. Faraday Soc.*, 1941, 37, 377.

¹² Stevenson, *J. Chem. Physics*, 1942, 10, 291.

¹³ Baughan, *Nature*, 1941, 147, 542.

* Baughan¹⁴ (*Nature*, 1941, 147, 542) has suggested that this value for the average bond energy is in error on account of the use of too low a value for the heat of sublimation of carbon. Herzberg¹⁵ supports the earlier view in *J. Chem. Physics*, 1942, 10, 306.

¹⁴ Herzberg, *J. Chem. Physics*, 1942, 10, 306.

Summary.

An attempt has been made to determine the C—I bond energy and its variations under the influence of various substituents by measuring the rates of pyrolysis of the compounds in question. Variations in bond energy are found to be very marked. For a number of simple hydrocarbons the previously known activation energy of the reaction $\text{RCl}_3 + \text{Na}$ appears to be proportional to the bond energy $R - I$, the proportionality factor being 0.28 in fair agreement with theory. Negative substituents depress the activation energy below the value corresponding to the bond energy.

The above experiments were carried out during the sessions 1938/9 and 1939/40. The authors wish to thank Dr. E. Warhurst and D. J. N. Haresnape for their help in constructing the apparatus. One of us (E. T. Butler) is indebted to the University of Wales for a Fellowship.

The University, Manchester.

THE ELASTICITY OF A NETWORK OF LONG-CHAIN MOLECULES. I.

By L. R. G. TRELOAR.

Received 21st October, 1942.

According to the kinetic theory of elasticity of rubber-like materials, originally propounded by Meyer, v. Susich and Valko,¹ and subsequently developed by Guth and Mark² and by Kuhn,³ the retractive force in stretched rubber is due to the thermal motions of the carbon atoms of the molecular chain. On the assumption of free (or effectively free) rotations about each of the C—C bonds, it is shown that in the absence of external restraints the molecule will take up a randomly-kinked form in which its average length (measured by the distance between its ends) is only a small fraction of the length of the fully extended chain. The statistical treatment of the problem^{2, 3} leads to a formula defining the probability of a given length in terms of the molecular parameters.

An extension of the treatment to a three-dimensional network of molecules, in order to account for the properties of a rubber in bulk, has been attempted by various authors, notably by Kuhn³ and by Wall.^{4, 5} Their results, however, are not in agreement. In the present paper the methods of Kuhn and of Wall are critically examined, and the source of the discrepancies between their results is demonstrated.

Wall's Treatment of Elongation.

In this discussion the historical order will be reversed, and Wall's work will be considered before that of Kuhn which appeared 8 years earlier.

Working on the basis of Kuhn's statistics of the individual molecule Wall set out to calculate the entropy of a network of N equal molecules making up a cylinder of length l_0 in the undeformed and l in the deformed state. For this structure the distribution of lengths (*i.e.* distances between

¹ Meyer, v. Susich and Valko, *Koll. Z.*, 1932, 59, 208.

² Guth and Mark, *Monat. Chem.*, 1934, 65, 93.

³ Kuhn, *Koll. Z.*, 1934, 68, 2; 1936, 70, 258.

⁴ Wall, *J. Chem. Physics*, 1942, 10, 132.

⁵ Wall, *Ibid.*, 1942, 10, 485.

junction points) of the molecules in the undeformed state was assumed to be that given by Kuhn's formula, which may be written

$$p(x, y, z) dx \cdot dy \cdot dz = \frac{\beta^3}{\pi^2} e^{-\beta^2(x^2 + y^2 + z^2)} dx \cdot dy \cdot dz \quad . \quad (1)$$

In this equation x , y and z represent the components of length of a given molecule along each of the three co-ordinate axes, and

$$\frac{1}{\beta^2} = \frac{2}{3} l_c^2 Z \frac{1 - \frac{1}{2} \cos \theta}{1 - \frac{1}{2} \cos \theta} \quad . \quad . \quad . \quad (1a)$$

l_c being the C-C bond distance, Z the number of links in the molecular chain, and θ the supplement of the valence angle. To describe the deformation Wall assumed that the volume remains unchanged, and that the components of length of each molecule change in the same ratio as the corresponding dimensions of the bulk rubber. Thus, writing α for l/l_0 , x , y and z are changed to αx , $\alpha^{-\frac{1}{2}} y$ and $\alpha^{-\frac{1}{2}} z$ respectively,* and the corresponding distribution function is

$$p'(x, y, z) dx \cdot dy \cdot dz = \frac{\beta^3}{\pi^2} e^{-\beta^2(\alpha^2/x^2 + \alpha^2/y^2 + \alpha^2/z^2)} dx \cdot dy \cdot dz \quad . \quad (2)$$

The problem is to determine the probability P that the assembly of N molecules should be found in the state represented by equation (2), when the probability that a given molecule has components of length x , y and z is given by equation (1). The result found by Wall is

$$\ln \frac{P}{P_0} = - \frac{N_0}{2} \left(\alpha^2 + \frac{2}{\alpha} - 3 \right) \quad . \quad . \quad . \quad (3)$$

where P_0 is the probability of the most probable distribution. The entropy change due to the extension is therefore

$$S = S_0 - k \ln P/P_0 = - \frac{1}{2} N_0 k \left(\alpha^2 + \frac{2}{\alpha} - 3 \right) \quad . \quad . \quad . \quad (4)$$

The tension T is then obtained by applying the thermodynamic relation

$$F = \left(\frac{\partial W}{\partial t} \right)_T = - T \left(\frac{\partial S}{\partial t} \right)_T \quad . \quad . \quad .$$

giving, for a cylinder of original cross-sectional area 1 cm.²,

$$F = NkT \left(\alpha - \frac{1}{\alpha^2} \right) = \rho \frac{RT}{M} \left(\alpha - \frac{1}{\alpha^2} \right) \quad . \quad . \quad . \quad (5)$$

where N is the number of molecules per c.c., M the molecular weight and ρ the density.

Equation (5) applies for a uni-directional compression as well as for an elongation.

2. Wall's Treatment of Shear.

A simple shear may be defined by a change of the dimensions of the specimen from x , y and z to αx , y/α and z .† As before Wall assumed that the molecular components of length change in the same ratio as the external dimensions. The function representing the distribution of molecular lengths in the state of shear is therefore

$$p'(x, y, z) dx \cdot dy \cdot dz = \frac{\beta^3}{\pi^2} e^{-\beta^2(\alpha^2/x^2 + \alpha^2y^2 + z^2)} dx \cdot dy \cdot dz \quad . \quad (6)$$

* In his earlier paper⁴ Wall took account only of changes in the z components of length. His later treatment,⁵ which is obviously the more correct, is here considered.

† Love, *Mathematical Theory of Elasticity*, Cambridge University Press, 2nd Ed. p. 34.

The result was obtained in terms of the work required to produce a shear deformation σ ($\alpha - \frac{1}{\alpha}$), namely

$$W = \frac{1}{2} N k T \sigma^2 = \frac{1}{2} G \sigma^2 \quad . \quad . \quad . \quad (7)$$

from which it is seen that the modulus of rigidity G appears as a constant. That is to say, the network obeys Hooke's law under shear, though not under elongation.

3. Kuhn's Treatment of Elongation.

Kuhn made the same fundamental assumptions as Wall, but worked from a consideration of the entropy of the single molecule, integrating over the whole assembly of molecules in order to obtain the total entropy. From equation (1) the entropy s of a single molecule is given by Kuhn as

$$s = k \ln p = c_1 - k \beta^2 (x^2 + y^2 + z^2) \quad c_1 = k \beta^2 r_1^2 \quad . \quad . \quad . \quad (8)$$

where r_1 is the distance between its ends. The contribution to the total entropy per c.c. due to molecules having length component, between x and $x + dx$, y and $y + dy$, z and $z + dz$ is obtained by multiplying this entropy s by the appropriate number of molecules, i.e.

$$s \cdot N p(x, y, z) dx \cdot dy \cdot dz \quad .$$

N being the number of molecules per c.c. Integration gives the total entropy S_1 corresponding to the unstretched state,

$$S_1 = \iiint_{-\infty}^{+\infty} N [c_1 - k \beta^2 (x^2 + y^2 + z^2)] \frac{\beta^3}{\pi^{\frac{3}{2}}} e^{-\beta^2(x^2 + y^2 + z^2)} dx \cdot dy \cdot dz \quad . \quad (9)$$

For the deformed state corresponding to an extension in the x direction of amount γ ($= l/l_0 - 1$) the entropy S'_1 is represented by the integral

$$S'_1 = \iiint_{-\infty}^{+\infty} N [c_1 - k \beta^2 (x^2 + y^2 + z^2)] \frac{\beta^3}{\pi^{\frac{3}{2}}} e^{-\beta^2(x^2/(1+\gamma)^2 + (y^2+z^2)(1+\gamma))} dx \cdot dy \cdot dz \quad (10)$$

in which the exponential term represents the distribution of molecular lengths after deformation. Integration of expressions (9) and (10) leads to the approximate relation

$$S'_1 - S_1 = \frac{3}{2} N k \gamma^2 \quad . \quad . \quad . \quad . \quad (11)$$

Entropy due to r_s and r_b Values. The entropy thus determined, referred to by Kuhn as the partial entropy due to the r_1 values, was not considered to represent the whole of the entropy change on extension. He argued that besides having a "length" r_1 , the molecule may be considered to have a "breadth" r_s and a "thickness" r_b , and that it is necessary to take into account also the partial entropies associated with the r_s and r_b values. If Z is the number of links in the chain, r_s is defined as the distance of the middle link from the line joining the ends, and r_b as the distance of links numbered $Z/4$ and $3Z/4$ (counting from one end of the chain) from the plane containing r_1 and r_s . Kuhn's method of calculating the entropy due to the r_s and r_b values will not be considered here. The result is that an additional entropy of amount $-Nk\gamma^2$ is introduced for each of these values, so that the total entropy change on extension becomes

$$S' - S_0 = -\frac{3}{2} N k \gamma^2 - 2 N k \gamma^2 = -\frac{7}{2} N k \gamma^2 \quad . \quad . \quad . \quad (12)$$

This leads directly to the stress-strain relation

$$F = 7 N k T \gamma = 7 N k T (\alpha - 1) \quad . \quad . \quad . \quad (13)$$

This result does not agree with that of Wall (equation (5)), the one relation being linear and the other non-linear. The reasons for this discrepancy will now be considered.

4. Criticism of Kuhn's Treatment.

The r_1 and r_2 Values.—The probability function (1) is derived by considering the number of possible configurations of the molecule when one end is fixed at the origin of co-ordinates and the other is contained within a small volume element $dx \cdot dy \cdot dz$. On Kuhn's basis the entropy is reduced on extension because the number of possible configurations is reduced. In stating the probability in terms of r_1 he includes all possible configurations, and therefore all possible values of r_1 and r_2 . The r_1 and r_2 values cannot be considered to have an existence independently of r_1 and to attribute a separate entropy to them is incorrect.

If the r_1 and r_2 values are omitted, equation (13) becomes

$$F = 3NkT\gamma \quad \dots \quad \dots \quad \dots \quad (14)$$

Wall's equation (5) gives for the modulus at zero extension

$$\left(\frac{dF}{dy}\right)_y = 3NkT \quad \dots \quad \dots \quad \dots \quad (15)$$

The modified formula (14) thus agrees with Wall's equation for sufficiently small elongations.

It will now be shown that the remaining difference between the results of Wall and of Kuhn is due to the introduction of an approximation by the latter author.

5. Amendment of Kuhn's Treatment.

(a) Elongation.—From Kuhn's equations (9) and (10) the entropy change on extension may be written

$$\begin{aligned} \frac{\pi^{\frac{3}{2}}}{Nk\beta^{\frac{3}{2}}} (S'_1 - S_1) &= \int \int \int_{-\infty}^{+\infty} (x^2 + y^2 + z^2) e^{-\beta^2(x^2 + y^2 + z^2)} dx \cdot dy \cdot dz \\ &- \int \int \int_{-\infty}^{+\infty} (x^2 + y^2 + z^2) e^{-\beta^2(x^2/(1+y)^2 + (y^2+z^2)(1+y))} dx \cdot dy \cdot dz \quad (16) \end{aligned}$$

Insertion of the appropriate values of the definite integrals * gives

$$\begin{aligned} \frac{\pi^{\frac{3}{2}}}{Nk\beta^{\frac{3}{2}}} (S'_1 - S_1) &\approx \frac{3}{2} \frac{\pi^{\frac{3}{2}}}{\beta^3} - \frac{\pi^{\frac{3}{2}}}{2\beta^3} \left[(1+y)^2 + \frac{2}{1+y} \right] \\ \text{or } \frac{1}{Nk} (S'_1 - S_1) &\approx \frac{3}{2} - \left[\frac{(1+y)^2}{2} + \frac{1}{1+y} \right] \approx \frac{1}{2} \left(\alpha^2 + \frac{2}{\alpha} - 3 \right). \quad (17) \end{aligned}$$

Equation (17) is identical with Wall's eqn. (4), and leads directly to the stress-strain relation (5), without any approximation. The approximation introduced by Kuhn (valid for small values of γ) was evidently to write

$$\frac{1}{1+\gamma} = 1 - \gamma + \gamma^2,$$

and thus to obtain

$$\frac{1}{Nk} (S'_1 - S_1) \approx -\frac{3}{2}\gamma^2 \quad \dots \quad (\text{cf. equation (11)})$$

* Jeans, *Dynamical Theory of Gases*, 3rd Ed. p. 435.

It is obvious that the formula of Kuhn is valid only for elongations of considerably less than 100 %. It is unfortunate that Kuhn did not emphasise the fact that an approximation was involved in the derivation of his apparently linear stress-strain relation.

(b) Shear. Although Kuhn did not deal with the shear deformation, this problem also may be dealt with by his method. Writing the total entropy after shearing in the form

$$S'_1 = \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} N |(\epsilon - k\beta^2(v + w + z))|^{\frac{1}{\alpha}} e^{-\beta(v^2 + w^2 + z^2)} dv dz dw \quad (18)$$

and following exactly the same process as in the case of elongation, we obtain

$$\frac{1}{Nk}(S'_1 - S_1) = \frac{1}{2}(\sigma^2 + \frac{1}{\alpha} - 2) + \dots \quad (19)$$

which, on substitution of σ for $\sigma - \frac{1}{\alpha}$, leads to Wall's result (equation (7))

$$W = \frac{1}{2}Nk/\sigma^2.$$

6. Some General Considerations.

The more accurate application of Kuhn's method thus leads to the same stress-strain relations as those derived by Wall. The two methods may be considered to be equivalent mathematically, since they differ only in the particular stage of the argument at which the conception of the entropy is introduced. Wall considered only the entropy to be associated with the whole assembly of molecules; Kuhn, on the other hand, considered that an entropy could be associated with the individual molecule. Wall's treatment must be considered the more satisfactory because it avoids the difficulties encountered in attempting to assign a physical meaning to the entropy of a single molecule.

An equation of similar form to (5) has been derived independently by Guth and James,⁶ who state that it represents the experimental data for both elongation and compression of rubber to a close approximation. In using the equations of the kinetic theory, however, it is important to keep in mind the assumptions which form their basis. In Kuhn's statistical treatment of the paraffin molecule, from which all the later developments have proceeded, it is assumed that the distance r is small compared with the unstretched length of the chain. The formulae derived from the network theory would therefore not be expected to apply to a state of deformation in which any important fraction of the molecules were nearly fully extended. They cannot therefore be expected to account accurately for the whole of the stress-strain curve of rubber.

It is interesting to note that equations (5) and (7) contain, implicitly, M , the "molecular weight" between junction points, but do not specifically contain Z , the number of links, or θ , the supplement of the valence angle (which are included in the parameter β (equation (1a))). The equations would therefore not be affected if the freedom of rotation about bonds were imperfect, since, as Kuhn has shown,⁸ a chain of Z links possessing hindered rotation is equivalent to a chain containing a smaller number Z/s of freely rotating links (where s is a small number), provided, of course, there are still enough effective links to justify the application of statistical methods. The same argument shows that the elastic properties of the network will not be affected by the presence of a proportion of non-rotating bonds, such as the C=C bond in rubber.

Summary.

The treatment of the elasticity of a molecular network by the method of Wall is discussed and compared with the earlier treatment of Kuhn. It is shown that a more accurate application of Kuhn's method leads to formulae for elongation and shear in agreement with those of Wall.

The author desires to acknowledge his indebtedness to Dr. J. K. Roberts, for several helpful discussions during the preparation of this paper, which forms part of the programme of fundamental research on rubber undertaken by the Board of the British Rubber Producers' Research Association.

REVIEWS OF BOOKS.

Spectroscopy and Combustion Theory. By A. G. GAYDON. (London : Chapman and Hall. Pp. x + 191. Price 17s. 6d. net.)

Our knowledge of what flame and combustion can say about atoms and molecules is far from complete. Much valuable qualitative work (e.g. the recognition of very short-lived chemical complexes) has been achieved, but far less in the quantitative field. Probably this is connected with the somewhat severe experimental difficulties encountered in the measurement of flame temperatures.

In the book now under review, the author stresses these points, and in the last chapter—perhaps the best in the book, for he is drawing upon his own extensive experience—goes on to indicate a number of ways in which the spectroscope can help in solving mechanical and chemical problems. It seems that much here attracts the attention of the chemical engineer. One suggestion is a greater use of photography in the region between 7000 Å and 10,000 Å. To judge from some recent factory literature on applied photography there is a reasonable prospect of a general development of technique for the photographic study of flames. It is certainly well worth encouraging.

A somewhat tantalising, but engaging topic, most interestingly discussed, is the possible existence of CO₂, or carbon peroxide. Experimental evidence is, in general, against it, but not quite conclusively. Crystallographers would rejoice if anything definite could be established, since this complex, in any state of matter, is so important for them.

The remainder of the book follows fairly conventional lines, in dealing with "knock," after-burn, predissociation and so forth. It is all useful enough, but shows a tendency—very difficult to avoid—to write round the references. There is a full bibliography, and a good deal of conveniently arranged tabular matter.

Although for what is little more than a manual the price is high, the format and illustrations are so good, that it is hard to believe that there is a war on.

Reports on Progress in Physics, Vol. VIII. Pp. iv + 372. London: The Physical Society, 1943. 25s.

An outstanding feature of this volume is that six of the fourteen reports which it contains come from the pens of American physicists who, as the Editor points out in the preface, gave unstinted help and support at a difficult time. Co-operation of this kind has not only enabled the size of the volume to be maintained, but has also made available descriptions of work carried out on that larger scale which is typical of American research laboratories.

Of the six articles referred to, the most valuable is that on the general physical constants, which gives the values, as at August, 1941, of all the physical constants together with their probable errors, special attention being given to the velocity of light. Another interesting report coming from overseas is on high speed centrifuging, in which the theory, design and performance of these centrifuges are described.

Spectroscopy still provides a fruitful field of progress, there being articles on its application to combustion, the mechanical measurement and tabulation of wavelengths, molecular electronic spectra, nuclear levels, and dispersion in the far infra-red. The last-named deals with dispersion in crystalline and liquid substances at wavelengths beyond 10μ and its interpretation in terms of internal structure and polarisation.

The usefulness of a volume such as this in making available to the average physicist authoritative accounts of new work with which he would not generally make contact is well illustrated in the articles on photometry, instrumental technique in astro-physics and friction between solid bodies. These articles deal with the progress of the last few years.

The high standard which the Physical Society has set itself has been well maintained and (to quote a phrase from one of the articles) a living and growing science is presented to the reader.

R. H. H.

Journal of the Electrodepositors Technical Society, Vol. XVII, 1941-42.

The Society at Northampton Polytechnic Institute, St. John Street, Clerkenwell, London, E.C. Price to non-members, 21s. Pp. 164, 8vo, including 26 plates.

The Society is to be congratulated on this evidence of continual growth and activity, despite the pre-occupation of so many members upon national duty. The volume contains six papers on metallic coatings or upon specific problems arising therefrom, and it also embodies the reports upon four useful discussions held during the session, *viz.* those upon "Silver Coatings on Non-metallic Surfaces," "Plating Problems under Present Conditions," "Problems Confronting Platers during War-time," and "M.A.P. Specifications and Tests." This record of work should encourage all who are interested not only to buy this volume, but to join the Society and receive it as of right next year.

The Faraday Society

Minutes of the 36th Annual General Meeting

Held on Saturday, 12th December, 1942, at 12 noon, at
the Hotel Rembrandt, Thurloe Place, London, S.W. 7

1. The Minutes of the 35th Annual General Meeting, which had been printed in the November, 1941, issue of the *Transactions*, were taken as read and confirmed.

2. The Annual Report and Statement of Accounts, together with the report of the Auditors for 1941, were presented by the Honorary Treasurer who, in submitting the Statement of Accounts, explained that the expenses were less owing to the war-time curtailment of activities. There had been little expense connected with meetings. The money saved was being invested from time to time and would be available to meet any possible future requirements. The fall in membership was due to the loss of enemy members; the non-receipt of subscriptions from members in occupied territories had temporarily affected revenue.

Membership.—The Meeting approved that after the war the Council should use its discretion as to whether enemy members would be taken back into the Society or not, but that non-enemy members in temporarily occupied territory should be retained on the rolls even though their subscriptions had not been paid.

War.—It was proposed by Dr. Bury, seconded by Dr. Goodeve, and unanimously approved that the Society should put on permanent record its gratitude and appreciation to Mrs. Tooth, the office cleaner, for the part she had played, at considerable risk to herself, in salvaging the Society's property on the 16th-17th of April, 1941, when the offices of the Society were destroyed by fire as a result of enemy action.

The Secretary, in amplifying the Report of Council with regard to the destruction of the offices of the Society, mentioned that with the exception of the current records and files, the typewriter and a complete set of the *Transactions*, all of which had been saved by Mrs. Tooth, all the property and old records of the Society were destroyed. With the co-operation of the Members, as a result of the personal message which was printed on the cover of the May, 1941, issue of the *Transactions*, the Society was able to carry on its work with little interruption in new offices which were taken at the present address. The work of reconstituting the Society was not easy, however, because in May, 1941, further destruction was caused in Gray's Inn by enemy action. As a result the offices occupied in April were for two or three months shared with a firm of solicitors who had lost the greater part of their premises and it was not until September of 1941 that the present convenient offices in the same building could be rendered available for the Society.

Student Members.—At Professor Ferguson's suggestion the Secretary was directed to make personal approach to the heads of departments asking them to encourage students to join the Society as Student Members.

Joint Payment of Subscriptions.—The Secretary mentioned that arrangements had been made with the Institute of Physics and the other

44 MINUTES OF 36TH ANNUAL GENERAL MEETING

participating societies to modify, as from 1st January, 1944, the scale of payment of joint subscriptions. An approach had been made to the Institute of Chemistry, offering a reduced subscription if paid to the Institute; further negotiations would be opened with the Joint Chemical Council. Such further co-operation with the chemical societies was welcomed by the meeting.

On the motion of the Honorary Treasurer, seconded by Professor Ferguson, the Report and Statement were adopted.

3. On the motion that the present Officers and Ordinary Members of Council should be re-elected for the session 1942-43, Dr. Bury and Professor Travers suggested that the time had come to revert to normal elections. After some discussion it was unanimously agreed that the present position be continued for the coming year. It was, however, agreed that before the next Annual General Meeting there should be an Extraordinary General Meeting to discuss policy and in particular to decide whether the Society should revert to its normal procedure of election.

It was proposed by the Honorary Treasurer and seconded by Professor Ferguson and agreed that at this Extraordinary General Meeting a short account should be given by the President on the position of the Society.

The Officers and Ordinary Members of Council to take office as from 1st October, 1942, were thereupon re-elected as follows :—

OFFICERS AND COUNCIL, 1943-1944.

President.

PROF. E. K. RIDEAL, M.B.E., D.Sc., F.R.S.

Vice-Presidents who have held the Office of President.

SIR ROBERT ROBERTSON, K.B.E., D.Sc., F.R.S.

PROF. F. G. DONNAN, C.B.E., Ph.D., F.R.S.

PROF. C. H. DESCH, D.Sc., F.R.S.

PROF. N. V. SIDGWICK, Sc.D., D.Sc., F.R.S.

PROF. M. W. TRAVERS, D.Sc., F.R.S.

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F.R.S.

Honorary Treasurer.

R. E. SLADE, D.Sc.

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Ordinary Members of Council.

E. J. BOWEN, M.A., F.R.S. F. D. MILES, D.Sc.

C. R. BURY, B.A. W. J. SHUTT, D.Sc.

J. J. FOX, C.B., O.B.E., D.Sc. D. W. G. STYLE, Ph.D.

PROF. W. E. GARNER, D.Sc., F.R.S. PROF. S. SUGDEN, D.Sc., F.R.S.

R. LESSING, Ph.D. O. J. WALKER, Ph.D.

This concluded the business of the meeting.

THE FLUORESCENCE OF PHENYLATED ANTHRACENES.

By Y. HIRSHBERG AND L. HASKILBORG.

Received 13th July, 1942.

In an investigation of the physical properties of the polycyclic hydrocarbons which are being synthesised in our laboratories, we have also studied their fluorescence, more especially the influence of substituents on the number, position and intensity of the fluorescence bands. In the following table the results obtained for a number of phenylated anthracenes are listed and compared with those for the parent substance, anthracene, which has frequently been investigated before.¹

TABLE.

Substance.	Band I.	Band II.	Band III.	Remark.
Anthracene . . .	max. at 4070	max. at 4290	max. at 4530	II very intense, I and III weaker
1-phenyl-anthracene . . .	4200	4410	—	I very intense, II weaker
2-phenyl-anthracene . . .	4200	4420	4630	I and II very intense, III weak
9-phenyl-anthracene . . .	4220	4500	4700	I and II intense, III slightly weaker
1,4-diphenyl-anthracene . . .	4490	—	—	Very intense
9,10-diphenyl-anthracene . . .	4200	4330	4580	II intensest; all bands rather diffuse
2,9-diphenyl-anthracene . . .	4320	4480	4520	I more intense, II weaker, III still weaker
1,4,9,10-tetraphenyl-anthra- cene . . .	4660	5050	—	I very intense, II weak
pseudo-1,4,9,10-tetra- phenyl-anthracone . . .	no fluo- rescence			
1,4,5,8-tetra-phenyl- anthracene . . .	4380	4515	—	II more intense than I

Inspection of the intensity curves as reproduced in Fig. 1, shows that every substitution in the anthracene system by a phenyl group increases the absolute intensity of fluorescence, and that mono-phenylation of anthracene in one of the three possible positions shifts the fluorescence bands in approximately the same way. It is interesting that 1-phenyl-anthracene has only two, not three bands—the more as in 1,4-diphenyl-anthracene only one broad band appears. In 9,10-diphenylanthracene, the shift is somewhat less marked, and one is inclined to ascribe that to its symmetrical structure, as compared, e.g. with 9-phenyl-anthracene. In general, the intensity distribution is so different in the different cases, that the fluorescence spectrum could be used for the identification of the various hydrocarbons. The relatively high fluorescence of the meso-phenylated hydrocarbons is conspicuous; this is to be expected as the

¹ See, e.g. Pringsheim, *Trans. Faraday Soc.*, 1939, 35, 28.

electrons in these positions are loosened by the phenyl groups. It is more surprising that 2-phenyl-anthracene shows a similar effect; perhaps this is also due to an influence of the phenyl group on the fluorescent meso-carbon atom, via a resonance form similar to that suggested in the case of diphenyl,^{2,3} which would involve one of the carbon bonds of the meso-ring.

Outstanding is the fluorescence spectrum of 1 : 4 : 9 : 10 : tetraphenyl-anthracene; the bands reach very far into the visible region of the spectrum, in accordance with the intense yellow colour of this hydrocarbon, which differs from anthracene not less than 9 : 10 : 11 : 12 : tetraphenyl-naphthalene (rubrene) from naphthalene.⁴ That the pseudo-compound, obtained from 1 : 4 : 9 : 10 : -tetraphenylanthracene by treatment with, e.g., formic acid, shows no fluorescence, concords well with either of the formulae discussed recently by Weizmann, Bergmann and Haskelberg,⁵ both representing dihydroanthracene derivatives.

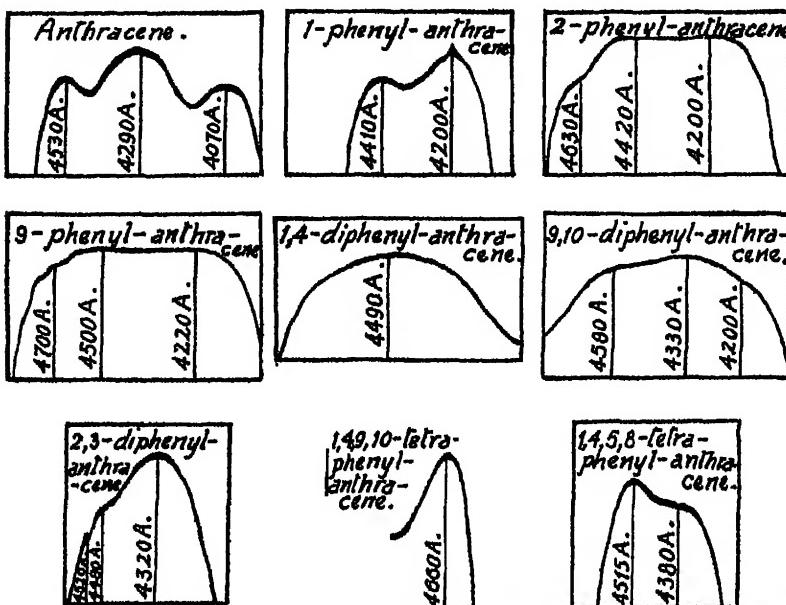


FIG. 1.

For theoretical reasons, one should expect dihydroanthracene derivatives to be non-fluorescent, but there are certain cases, where fluorescence has been reported^{6,7,8} and which most probably need re-investigation.

² Le Févre and Le Févre, *J. Chem. Soc.*, 1936, 1130.

³ Lennard-Jones and Turkevitch, *Proc. Roy. Soc., London A*, 1937, 158, 297.

⁴ Absorption of naphthalene, Radulescu and Barbulescu, *Z. physikal. Chem., B*, 1929, 5, 177; Clar, *Ber.*, 1936, 69, 607. Absorption of rubrene; Willemart, *Compt. Rend. Acad. Sci.*, 1929, 188, 988; Badoche, *Ann. chim. (10)*, 1933, 20, 200; Dufraisse and Girard, *Bl. Soc. Chim. France* (5), 1935, 1, 1359; Dufraisse and Badoche, *Compt. rend. Acad. Sci.*, 1935, 200, 929. For the fluorescence spectra see: Radulescu and Barbulescu, *J.C.*; Radulescu and Dragalescu, *Bl. Soc. Chim. România*, 1925, 17, 9; Dhére and Raffy, *Compt. Rend. Acad. Sci.*, 1935, 200, 386; *Bull. Soc. Chim. France* (5), 1935, 2, 1424.

⁵ Weizmann, Bergmann and Haskelberg, *J. Chem. Soc.*, 1939, 391.

⁶ Barnett and Matthews, *J. Chem. Soc.*, 1923, 123, 380.

⁷ Matthews, *J. Chem. Soc.*, 1926, 120, 236.

⁸ Schlenk and Bergmann, *Liebig's Annalen*, 1928, 463, 148.

In the case of $1:4:5:8$ -tetraphenyl- $9:10$ -dihydroanthracene, we have observed a marked fluorescence, which, however, corresponds exactly with that of $1:4:5:8$ -tetraphenyl-anthracene, both with regard to position and to relative intensity of the fluorescence bands. We believe, therefore, that the dihydro-compound contains traces of the non-hydrogenated substance, and it may well be that the observed rather high absolute intensities are due to the high dilution, while in slightly greater concentration a quenching effect occurs (see e.g. Pringsheim, *I.c.*).

We wish to express our gratitude to Dr. Friedla Goldschmidt, who has carried out the photo-micrographic evaluation of the band intensities.

Experimental.

(a) Materials.—*Anthracene*, the purest commercial sample, was recrystallised repeatedly from butyl acetate. It formed colourless crystals, exhibiting an intense blue fluorescence. $9:10$ -Diphenylanthracene, m.p. 247° , was prepared according to Schlenk and Bergmann.⁸ *1-Phenyl-anthracene*, $1:4$ -diphenylanthracene, $1:4:9:10$ -tetraphenylanthracene and its pseudo-derivative were the samples, previously obtained by Weizmann, Bergmann and Haskelberg.⁹ For the preparation of 9 -phenylanthracene, the method of Krollpfeiffer and Branscheidt,¹⁰ interaction between anthrone and phenylmagnesium bromide, was considerably improved by using lithium phenyl, which does not cause as much enolisation as the Grignard compound.

In the same way, the hitherto unknown $2,9$ -diphenylanthracene was prepared: To a filtered solution of lithium phenyl (prepared from $10\cdot4$ c.c. bromobenzene and $1\cdot5$ g. lithium turnings) in anhydrous ether, 2 -phenyl-anthrone-(9)¹⁰ ($4\cdot8$ g.) was added in small quantities. After 12 hours, the reaction product was poured into ice-cold sulphuric acid and the ethereal layer washed, dried and evaporated. The residue was recrystallised from butyl acetate. Clusters of yellowish needles, m.p. $165-166^\circ$, exhibiting an intense blue fluorescence in solution. Yield, $3\cdot2$ g. (found: C, $94\cdot3$; H, $5\cdot1$. Calc. for $C_{22}H_{18}$: C, $94\cdot3$; H, $5\cdot5$ %).

2-Phenyl-anthracene was obtained from the same 2 -phenyl-anthrone by reduction with zinc dust and ammonia in presence of platinum chloride.¹¹ M.p. 207° .¹¹

$1:4:5:8$ -Tetraphenyl- $9:10$ -dihydro-anthracene. After some failures, we eventually succeeded in reducing $1:4:5:8$ -tetraphenyl-anthraquinone¹² by the following method: The quinone (3 g.) was heated with red phosphorus ($0\cdot6$ g.) and hydroiodic acid (b.p. 127° , $3\cdot6$ c.c.) at $150-160^\circ$ for 6 hours in a sealed tube. The reaction product was treated with water, filtered, dried and recrystallised from amyl acetate. Prisms, m.p. $208-270^\circ$; yield, $2\cdot1$ g. (found: C, $93\cdot6$; H, $5\cdot9$. Calc. for $C_{26}H_{20}$: C, $94\cdot2$; H, $5\cdot8$ %). As pointed out above, the substance was not completely free from the following dehydrogenated compound.

$1:4:5:8$ -Tetraphenyl-anthracene. The foregoing hydrocarbon ($0\cdot125$ g.) was heated at 240° with sublimed sulphur ($0\cdot5$ g.), until the evolution of hydrogen sulphide ceased. The reaction product was treated with carbon disulphide, which dissolved the excess sulphur, and the residue ($0\cdot12$ g.) recrystallised from bromobenzene and sublimed in a high vacuum. Yellow needles, m.p. 370° . The solutions exhibit a strong violet-blue fluorescence (found: C, $94\cdot4$; H, $5\cdot4$. Calc. for $C_{26}H_{20}$: C, $94\cdot6$; H, $5\cdot4$ %).

(b) Methods.—The measurements reported have been carried out with the fluorescence microscope of Haftinger;¹³ the substances were

⁸ Krollpfeiffer and Branscheid, *Ber.*, 1923, **56**, 1617.

¹⁰ Scholl and Neovius, *Ber.*, 1911, **44**, 1075.

¹¹ Schlenk and Bergmann, *Liebig's Annalen*, 1928, **463**, 163.

¹² Cook, *J. Chem. Soc.*, 1930, 1087.

¹³ Haftinger, *Die Fluoreszenzanalyse in der Mikrochemie*, Vienna and Leipzig, 1937.

dissolved in purest benzene which did not show any fluorescence in the region investigated. The iron arc light passed a 10% solution of cupric sulphate and a Wood filter; then it was concentrated on the U.V. glass mirror of the microscope. Through the condenser the light was transmitted to the solution, which was contained in a quartz cuvette and had a concentration of 0.1-0.2%. All ultra-violet light, not absorbed by the substance, was destroyed by passing it through a glass cuvette, containing an aqueous 5% solution of sodium nitrite, so that only the fluorescence light could reach the objective of the microscope and from there the micro-spectrograph which was fitted to the microscope instead of an eye-piece. The spectrum was photographed on plates of the size 4! x 6 cm.; on the same plates for comparison purposes was photographed a known spectrum, e.g., sodium, hydrogen or helium. The time of exposure varied from 4 to 6 hours.

All our experiments were checked by a macroscopic method, which utilised besides the Haizinger iron electrodes a mercury or a carbon arc as source of light. The light was concentrated on the substance by means of a quartz lens and the fluorescence beam, isolated as above, transmitted into the spectrograph (plates 6½ x 9 cm.). With concentrations down to 0.008%, the time of experiment required for this arrangement is 30 minutes. The results obtained with both these arrangements were identical throughout.

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VISCOSITY OF PURE LIQUIDS.

I. NON-POLYMERISED FLUIDS.

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Studies of viscous flow suggest that each unit act of flow requires an energy of activation.¹ In this respect it resembles diffusion in solids² or liquids,³ relaxation phenomena,⁴ or chemical reactions. A complete theory of the liquid state would enable E_A , the energy of activation, to be calculated independently of experiment, and it is noteworthy that in the allied rate processes of diffusion in solids⁵ and chemical kinetics⁶ this has been attempted with moderate success. E_A may, as the next most fundamental procedure, be measured by experiment, and calculations of the constants of diffusion (D), viscous flow (η), or chemical reaction (k) made in terms of it. This quasi-

¹ H. Eyring, *J. Chem. Physics*, 1936, 4, 283. A. G. Ward, *Trans. Faraday Soc.*, 1937, 33, 88.

² Barrer, *Diffusion in and through Solids*, Camb. Univ. Press, 1941, Chap. VI.

³ Glasstone, Laidler and Eyring, *Theory of Rate Processes*, McGraw-Hill Book Co., 1941, p. 522.

⁴ Ref. ², p. 544.

⁵ H. Huntingdon and F. Seitz, *Physic. Rev.*, 1942, 61, 375. H. Huntingdon, *ibid.*, 325. W. Jost, *J. Chem. Physics*, 1933, 1, 466.

⁶ Ref. ², Chap. III.

fundamental method has been applied with success by either of two methods :

- (1) The kinetic-statistical treatment.⁷
- (2) The transition state treatment.⁸

These procedures both accept an experimental energy of activation and then express all other components of D , η , or k from the theory.

As a starting-point in using these methods it is convenient to express data in terms of the Arrhenius equations :

$$\begin{aligned} k &= k_0 e^{-E_A/RT} \\ D &= D_0 e^{-E_A/RT} \\ \eta &= \eta_0 e^{E_A/RT}. \end{aligned}$$

Methods (1) and (2) then give specific values of k_0 , D_0 , and η_0 which may be compared with the experimental ranges of values. Progress in interpreting viscous flow by the kinetic-statistical method has been made,⁹ but the latter has not previously been applied to flow phenomena in simple and associated liquids. The purpose of this paper is to analyse and discuss experimental features of a diversity of flow systems in terms of the Arrhenius equation, and to obtain a general background covering their behaviour, according to current theory, and especially treatment (1) above. Accordingly the premises and predictions of the zone (kinetic-statistical) theory of viscous flow and diffusion⁹ are first briefly presented.

Zone Theory of Viscous Flow and Diffusion.

The initial premises of this theory⁹ are :

(1) The energy of activation (E_A) is not normally localised in one or two degrees of freedom unless E_A/T is small, but is distributed over a zone of degrees of freedom within the liquid. The larger is E_A/T the greater is the zone of activation. The absorption of E_A loosens the liquid in this zone as a pre-requisite for viscous flow or diffusion.

(2) Synchronisation or co-operation may still be needed between rotations or intermolecular vibrations before the unit act of flow or diffusion can occur.*

(3) Maxwell-Boltzmann statistics may be applied regionally to the liquid.

The calculation of viscosity and diffusion constants in rubber has already been made,⁹ and little modification is needed for molecular liquids. In a chain polymer the activated zone will consist of several tangled segments of chain belonging usually to different molecules, momentarily loosened by absorption of E_A . In a molecular fluid, the zone consists of a number of separate adjacent molecules similarly loosened. Only rotations and intermolecular vibrations need be considered in each case unless E_A is very great.†

The following predictions are based on this theory :

(1) $-\log \eta_0$ and E_A (or $\log D_0$ and E_A) should be functionally related for any series of liquids at constant temperature. The slopes of these curves should be governed primarily by the temperature rather than by the nature of the fluid (see p. 55 and Fig. 5). The curves of

* This was allowed for as the constant ρ of ref. *, p. 328, but is considered in more detail in the present paper.

† As for silicate glasses (Part II).

⁷ R. M. Barrer, *Trans. Faraday Soc.*, 1941, 37, 590; *ibid.*, 1942, 38, 322; also ref. *, Chap. VI.

⁸ H. Eyring, *J. Chem. Physics*, 1936, 4, 283. R. M. Barrer, *Trans. Faraday Soc.*, 1942, 38, 78.

⁹ R. M. Barrer, *Trans. Faraday Soc.*, 1942, 38, 322.

$\log D_0$ vs. E_A should all have a common origin. The curves of $-\log \eta_0$ vs. E_A , however, will have intercepts on the axis of $-\log \eta_0$ separated approximately by $\log T_1/T_2$ at two temperatures T_1 and T_2 . The slopes of these curves should increase as T decreases (Fig. 5 and p. 55).

(2) If the diffusion data refer to different temperatures and $\log D_0$ is plotted against E_A/T a universal curve should be obtained. When $-\log \eta_0$ is plotted against E_A/T all curves should be parallel, but displaced approximately by the factor $\log T_1/T_2$ for two sets of data at temperatures T_1 and T_2 . The low temperature data should be uppermost (see Fig. 6 and p. 55).

(3) $-\log \eta_0$ is a function of the zone size existing in the activated state. It is therefore in part a measure of the extent of the disturbance or the amount of loosening in the activated state. It is related to the entropy of activation of the transition state treatment, which should, however, as a result of premises (1) and (2) be composed of two terms, one depending primarily on E_A/T and the other primarily on the amount of synchronisation or co-operation necessary before a successful unit process can occur (see p. 56 and Table II).

The Data.

Viscosity data are presented in Table I (i) to (v), in terms of the Arrhenius equation, for the following classes of fluid:

- Liquid permanent gases;
- Liquid hydrocarbons and other apolar fluids;
- Polar liquids;
- Hydrogen and hydroxyl bonded liquids;
- Liquid metals;
- Simple ionic liquids.

The data cover the temperature ranges 60° K. to 1700° K.

TABLE I.

Substance	$-\log \eta_0$ (η_0 in poise).	E_A (e.v./mol. of unit process).	Temp. Range in °K.	Mean Value of E_A/T .	Index No. in Tables 5 and 6.	Refer- ence.
(i) Apolar Liquids and Liquid Permanent Gases.						
Oxygen	1.70	400	14.8-90°	5.60	6	10
Nitrogen	4.11	468	6.34-77.4	6.51	9	10
Carbon monoxide	4.01	461	6.02-81.2	6.54	8	10
Argon	3.90	544	8.1-87.5	6.11	7	10
Methane	4.47	740	10.3-14.8	7.36	10	10
Ethylene	3.60	710	10.3-16.9	5.40	5	10
n-Butane	3.82	1,417	14.9-29.6	5.18	11	11
n-Pentane	3.83	1,545	23.2-39.6	5.17	4	11
n-Hexane	3.83	1,780	27.3-31.5	5.04	1	11
n-Heptane	3.84	1,965	27.0-31.5	5.11	17	11
n-Octane	3.89	2,125	27.3-25.3	5.74	2	11
Benzene	3.96	2,490	27.3-34.3	8.08	13	11
m-Xylene	4.29	3,025	38.2-75.4	7.65	15	11
o-Xylene	4.34	3,265	38.9-61.4	8.13	16	11
Decahydronaphthalene	2.94	2,120	29.8-34.8	6.56	12	11
Carbon tetrachloride	4.07	2,760	27.3-6-34.7-16	8.86	18	11
Tetrachloroethylene	3.49	2,940	27.3-39.0	5.86	19	11
Isobutane	3.64	2,350	27.3-30.3	5.38	—	11
2 : 2 Dimethyl butane	3.94	8,030	27.3-30.3	7.05	1	11
2 : Methyl pentane	3.84	1,770	27.3-61-32.6-43	5.89	—	11
3 : Methyl pentane	3.68	1,610	27.3-30.3	5.39	—	11

¹⁰ A. G. Ward, ref. ¹.

¹¹ International Critical Tables, Vol. V, p. 10; Vol. VII, p. 211.

TABLE I—Continued.

Substance.	-Log η_0 (η_0 in poles).	E_A (cal./mol. of unit processes).	Temp. Range in °K.	Mean Value of E_A/T .	Index No. in Figs. 5 and 6.	Refer- ence.
(II) Polar Liquids.						
Carbon disulphide	3.39	1,380	273-435-46	4.32	8	xx
Sulphur dioxide	3.43	1,300	230-5-273-9	5.07	10	xx
Acetone	3.89	1,850	183-3-273	8.12	7	xx
Acetone	3.75	1,700	280-80-356-86	5.49	26	xx
Methyl ethyl ketone	3.61	1,930	273-32-319-75	3.98	9	xx
Diethyl ketone	3.83	4,020	273-4-6-371-82	6.28	33	xx
Nitrosoyl chloride	4.19	2,350	230-7-253	9.11	31	xx
Dimethyl sulphate	4.97	3,010	273-340-5	9.75	17	xx
Phenyl isocyanide	3.70	1,390	273-1-151	6.94	5	xx
Phenyl chloride	3.74	2,110	273-30-246	6.05	6	xx
Pyridine	3.70	2,350	273-384	6.97	29	xx
Quinoline	4.58	3,970	282-8-313	11.32	11	xx
Quinoline	3.51	2,560	308-145	6.05	15	xx
Diethyl aniline	4.56	3,030	273-5-293	13.0	27	xx
Diethyl aniline	4.01	3,080	311-377	8.73	28	xx
Benzyl benzoate	6.58	7,500	278-288	16.5	40	xx
Benzyl benzoate	4.01	3,830	353-173	11.6	41	xx
N-Methyl diphenylamine	6.23	6,870	282-8-293-1	23.0	31	xx
N-Methyl diphenylamine	4.26	4,975	333-353	11.0	33	xx
Bromo	4.38	4,350	208-373	11.7	30	xx
Stannic chloride	3.35	1,175	313-343	4.35	13	xx
Methyl formate	3.07	1,610	273-58-302-35	5.70	34	xx
Methyl acetato	3.79	1,840	273-14-295-77	6.17	35	xx
Methyl propionate	3.81	1,980	273-38-296-46	6.96	36	xx
Methyl propionate	3.63	1,730	260-46-312-49	5.42	—	xx
Methyl butyrate	3.88	2,210	273-38-372-28	6.86	—	xx
Methyl octoate	4.12	3,050	298-343	9.82	37	xx
Methyl laurate	4.34	3,070	298-323	12.16	31	xx
Ribyl propionate	3.86	2,240	273-39-362-60	6.74	25	xx
Ribyl n-butyrate	3.86	2,270	298-343	7.08	24	xx
Ribyl n-valerate	4.08	3,090	298-343	8.07	28	xx
Ribyl pelargonate	4.12	3,120	298-383	10.35	16	xx
Ribyl laurate	4.80	4,410	298-323	14.20	30	xx
Ribyl bromide	3.59	1,600	273-34-304-15	5.48	2	xx
Propyl bromide	3.54	1,820	273-45-340-46	5.04	1	xx
Ribyl iodide	3.51	1,720	273-28-344-33	5.59	3	xx
Propyl iodide	3.58	1,950	273-30-372-80	6.06	4	xx
Ether	4.14	1,010	103-223	20.15	21	xx
Ether	3.80	1,370	213-273	14.46	13	xx
Ether	3.68	1,430	273-303	4.97	22	xx
Iodine	2.95	2,350	389-451-7	5.42	39	xx
Chlorine	3.21	882	296-5-210-3	4.05	38	xx
(III) Hydroxyl- and Hydrogen-bonded Liquids.						
Water	5.37	4,330	273-293	16.61	6	xx
Water	4.93	9,940	203-323	23.07	—	xx
Water	4.42	3,470	313-373	9.53	—	xx
Sulphuric acid	4.96	5,940	303-363	17.84	39	xx
Bromal hydrate	22.67	15,770	313-393	40.60	22	xx
Acetamide	4.75	4,980	378-393	12.92	23	xx
Urethane	5.92	5,660	333-353	16.50	46	xx
Urethane	4.87	4,930	353-393	13.83	—	xx
Methyl carbamate	5.79	6,890	324-6-347-6	18.60	45	xx
Methyl alcohol	4.24	2,350	273-333	8.41	3	xx
Ethy alcohol	4.49	3,440	273-343	11.28	5	xx

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TABLE I.—Continued.

Substance.	$-\log \eta_0$ (η_0 in poise).	E_A (cal./mole. of unit process ^a).	Temp. Range in °K.	Mean Value of E_A/T .	Index No. in Figs. 5 and 6.	Refer- ence.
(iii) Hydroxyl- and Hydrogen-bonded Liquids—(continued).						
<i>n</i> -Propyl alcohol	4.94	4,110	280-35-368-6	1.170	7	11
<i>n</i> -Butyl alcohol	4.90	4,650	273-17-387-11	1.105	8	11
<i>n</i> -Octyl alcohol	5.68	6,220	208-323	20.02	30	11
<i>n</i> -Orctyl alcohol	5.36	5,710	323-363	16.75	31	11
Cetyl alcohol	6.44	8,320	323-363	24.34	19	11
<i>iso</i> -Propyl alcohol	5.30	5,320	273-36-351-09	16.65	34	11
Secondary butyl alcohol	5.63	5,700	273-45-311-16	19.50	—	11
Secondary butyl alcohol	5.34	5,370	311-16-347-61	16.90	31	11
<i>t</i> -Butyl alcohol	8.17	9,360	205-41-322-99	34.13	9	11
<i>t</i> -Butyl alcohol	6.32	6,640	322-90-350-05	19.65	32	11
<i>t</i> -Amyl alcohol	7.82	8,750	273-49-208-01	30.65	35	11
<i>t</i> -Anyl alcohol	6.77	6,460	344-01-369-70	18.05	36	11
Formic acid	4.58	3,800	280-59-297-16	13.75	4	11
Formic acid	4.02	3,020	329-30-370-22	8.63	—	11
Acetic acid	3.92	2,680	303-86-310-46	8.45	2	11
Acetic acid	3.82	2,530	357-53-385-57	6.81	—	11
Propionic acid	3.85	2,540	277-70-410-05	7.02	1	11
<i>n</i> -Butyric acid	4.80	3,420	276-31-304-83	11.05	24	11
<i>n</i> -Butyric acid	3.98	2,950	388-44-428-76	7.28	25	11
Caproic acid	4.38	3,900	289-1-323	12.75	44	11
<i>n</i> -Heptylic acid	4.34	4,000	290-5-323	13.05	28	11
<i>n</i> -Heptylic acid	4.24	3,860	323-363	11.25	—	11
<i>n</i> -Caprylic acid	4.34	4,100	323-363	11.95	29	11
Paleronic acid	4.63	4,770	293-323	15.46	—	11
Paleronic acid	4.57	4,580	323-363	13.35	27	11
Caproic acid	4.42	4,540	323-343	13.65	26	11
Lauric acid	4.68	5,260	323-363	14.92	43	11
Myristic acid	4.64	5,370	333-363	15.42	42	11
Palmitic acid	4.64	5,570	343-363	15.50	43	11
Sterio acid	4.79	5,970	343-363	16.90	40	11
Phenol	7.01	8,200	291-3-313-2	27.10	11	11
Phenol	5.70	6,310	313-2-313-1	19.22	—	11
<i>o</i> -Cresol	9.34	11,400	273-381	41	10	11
<i>o</i> -Cresol	4.55	4,480	353-343	11	13	11
<i>m</i> -Cresol	10.60	13,100	273-483	48.5	17	11
<i>m</i> -Cresol	4.97	5,850	353-343	14.25	14	11
<i>p</i> -Cresol	10.87	13,100	273-483	50	18	11
<i>p</i> -Cresol	4.95	5,850	353-343	14.25	13	11
<i>o</i> -Hexahydrocresol	6.03	7,900	312-1-338-4	24.25	37	11
<i>o</i> -Hexahydrocresol	6.06	7,420	358-9-363	20.60	38	11
Menthil	8.86	11,600	307-9-349-9	36.33	12	11
Glycol	8.86	12,720	293	43.3	10	11
<i>o</i> -Toluindine	6.85	7,360	273-31-483	26.5	20	11
<i>o</i> -Toluindine	4.22	3,680	323-373	10.10	12	11
(iv) Liquid Metals.						
Mercury	2.23	598	273-373	1.85	2	10
Sodium	2.67	960	573-436	2.32	6	10
Potassium	3.01	1,150	573-473	2.71	7	10
Silver	2.24	4,870	1273-1523	3.48	10	10
Zinc	2.38	8,920	723-973	3.90	8	10
Cadmium	2.18	1,585	623-873	4.12	1	10
Tin	2.33	1,603	574-1013	4.02	3	10
Lead	2.39	2,320	623-1117	2.67	9	10
Antimony	2.54	2,920	973-1273	2.48	3	10
Bismuth	2.42	1,725	577-873	2.36	4	10

TABLE I—Continued.

Substance.	-Log η_0 (η_0 in poise).	E_A (cal./mol. of unit processes).	Temp. Range in °K.	Mean Value of F_A/F .	Index No. in Figs. 3 and 6	Refer- ence.
(v) Ionic Liquids.						
Sodium chloride	. . .	3.71	9,400	1114-1197	8.11	9
Sodium bromide	. . .	4.00	10,630	1015-1031	10.2	12
Sodium nitrate	. . .	2.81	3,410	481-690	5.38	5
Sodium hydroxide	. . .	3.32	5,470	623-643	8.12	12
Potassium chloride	. . .	3.15	7,830	1043-1308	6.61	6
Potassium bromide	. . .	3.53	7,960	1018-1078	7.61	6
Potassium nitrate	. . .	3.12	4,470	620-779	6.40	2
Potassium hydroxide	. . .	3.01	6,130	673-873	7.04	12
Potassium dichromate	. . .	3.07	6,740	670-780	8.30	12
Silver bromide	. . .	3.07	5,120	882-961	5.88	3
Silver bromide	. . .	3.84	4,540	961-1026	4.46	—
Silver iodide	. . .	2.96	5,810	878-1100	5.91	2
Silver nitrate	. . .	3.78	3,230	517-623	5.71	4
Lead chloride	. . .	3.46	7,780	771-881	10.72	14
Lead bromide	. . .	3.54	7,170	615-763	9.42	15
Ruthenium chloride	. . .	3.52	4,960	533-613	8.05	12
Lithium nitrate	. . .	3.69	5,970	513-537	10.92	16
Lithium nitrate	. . .	3.21	4,770	537-593	8.31	17

Relationships in Homologous Series.

In an homologous series of esters, acids, alcohols or hydrocarbons the data show that both E_A and $-\log \eta_0$ increase as the molecular weight increases. These data have been extended (for E_A) to very high molecular weight hydrocarbons,¹² for which it was suggested that E_A tends to a limiting value. Fig. 1 shows E_A as a function of chain length for several homologous series. In every series E_A increases less and less rapidly as the chain length grows, and there seems little doubt that with esters, alcohols and acids as with hydrocarbons E_A tends to a limiting value. This limiting value may be different in the various series. The ratio of E_A for ester, alcohol or acid to E_A for hydrocarbons is seen from Fig. 1 to tend to a constant value as the chain length rises.

The increment in E_A over that for hydrocarbons, when polar groups are introduced, is in the order



It is seen that the E_A vs. chain length curves of Fig. 1 actually diverge somewhat with increasing chain length; i.e. the increment in E_A increases with growing chain size. Another unusual feature is the well-defined minimum at propionic acid in the curve for fatty acids. The abnormality of formic and acetic acids is probably a result of particularly strong hydrogen bond interaction, which is a maximum with formic acid. In the molecule I it is thus likely that both H-atoms (1) and (2) can form hydrogen bonds.



The Magnitude of E_A .

Data of Table I (iii) and Fig. 1 show that E_A is very large for the alcohols, and considerably greater than for the acids. It is inferred that a high degree of co-ordinated structure must occur in such hydroxyl bonded fluids, and that this structure must undergo considerable local

¹² W. Kauzmann and H. Eyring, *J. Amer. Chem. Soc.*, 1940, 62, 3113.

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breakdown before the unit act of flow occurs. Moreover, for the lower molecular weight alcohols the values of E_A increases in the order :

Primary Alcohols < Secondary Alcohols < Tertiary Alcohols.

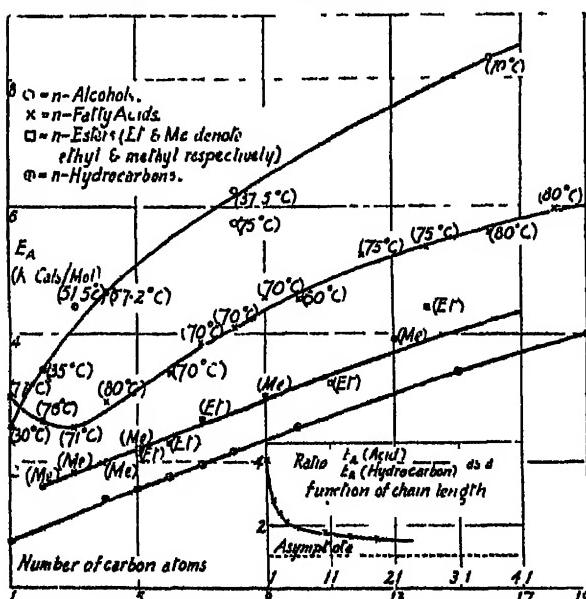


FIG. 1.—Relation between E_A and chain length for some homologous series.

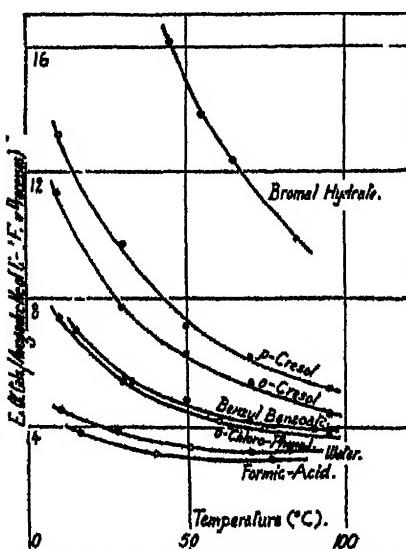


FIG. 2.— E_A as a function of T for certain liquids.

E_A is especially large for aromatic molecules containing hydroxyl groups, or for aliphatic molecules with several hydroxyl groups. Frequently E_A may compare with that for certain chemical reactions. In this connection the cresols, menthol, glycerol and bromal hydrate are notable. When E_A is very large it is frequently found that it decreases asymptotically as the temperature rises (Fig. 2). Rise in temperature causes a breakdown in the low

temperature structure in the liquid, so that the unit acts of viscous flow take place without the need of first breaking down an existing structure.

In ionic melts, E_A is often considerable, again indicating a degree of structure in the liquid. There is a strong tendency in such a fluid for positive ions to be co-ordinated by negative ions and vice versa, rather than for a purely random array of ions. Thus the unit act of flow involves an ionic cluster, which undergoes breakdown only when the cluster has absorbed considerable energy.

Properties of η_0 .

When $-\log \eta_0$ is plotted against the chain length for an homologous series, the value of $-\log \eta_0$ increases but at a diminishing rate, as the molecular weight rises (Figs. 3 and 4). $-\log \eta_0$ may eventually reach a

* For diagrams showing how this may happen, see ref. 1, Figs. 1 and 2, where the analogous problem of place exchange in solids is considered.

limiting size for very long molecules, which would mean that the activated zone tends towards a limiting size for very long molecules.

When $-\log \eta_0$ is plotted against E_A at constant T , a nearly linear relation is always found.* These linear relations have been previously indicated, and their significance discussed.⁸ They denote increasing zone size with increasing E_A . As E_A tends to a limit, so does $-\log \eta_0$ for any homologous series.

When $-\log \eta_0$ is plotted against E_A for several series of liquids at different values of T , the linear relations have slopes which increase as T decreases. A great many fluids covering the temperature ranges 60°K . to 1700°K . are included in Fig. 5, which serves to demonstrate this relationship. The nature of the molecular forces involved does not appear to be important. It will be noted that this behaviour is in accord with the zone theory (see p. 49).

Moreover, when $-\log \eta_0$ is plotted against E_A/T , the slopes for all fluids should be the same (p. 49).

The intercepts made on the $-\log \eta_0$ axis when E_A tends to zero should differ approximately by $\log T_1/T_2$ for data at temperatures T_1 and T_2 , respectively (see p. 49). Except at very low and very high temperatures,

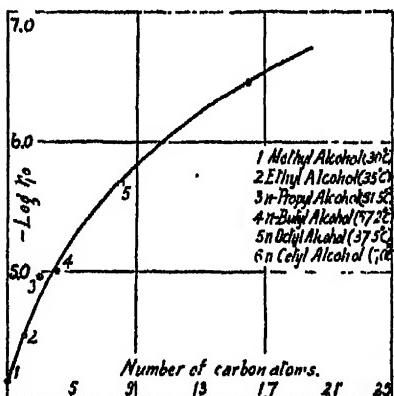


FIG. 3.—Relation between $-\log \eta_0$ and number of carbon atoms for some n -alcohols.

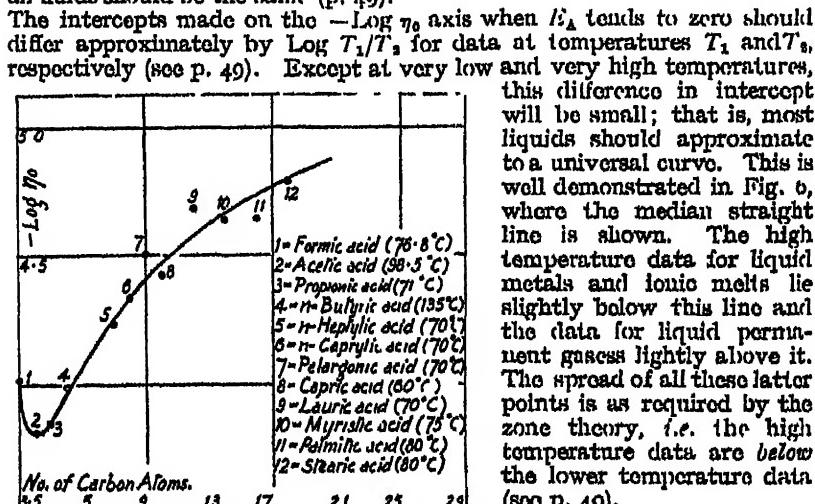


FIG. 4.—Relation between $-\log \eta_0$ and number of carbon atoms for some n -acids.

$$-\log \eta_0 = 2.43 + 0.167 E_A/T \quad (1)$$

Accordingly,

$$\eta_0 = 3.71 \times 10^{-8} e^{-0.77 E_A/RT} \text{ poises}, \quad (2)$$

$$\text{and} \quad \eta = 3.71 \times 10^{-8} e^{0.23 E_A/RT} \text{ poises} \quad (3)$$

The viscosity of any particular liquid may then be given as

$$\eta = k \cdot 3.71 \times 10^{-8} e^{0.23 E_A/RT} \text{ poises} \quad (4)$$

* This linear form may be predicted by the zone theory, as is shown in the next paper (Pt. II).

The equation of the median line is

where k allows for any deviation of that liquid from the universal equation (3). In some liquids it has been shown that E_A is a function of T (Fig. 2), and then E_A and k appropriate to the temperature range considered are to be used in the equation (4).

When the equations of the previous paragraph are compared with those of the transition state method, one has

$$\eta_0 = \frac{Nh}{1'} e^{-\frac{E_A}{RT}} = k \cdot 3.71 \times 10^{-3} e^{0.77E_A/RT} \text{ poises} \quad (5)$$

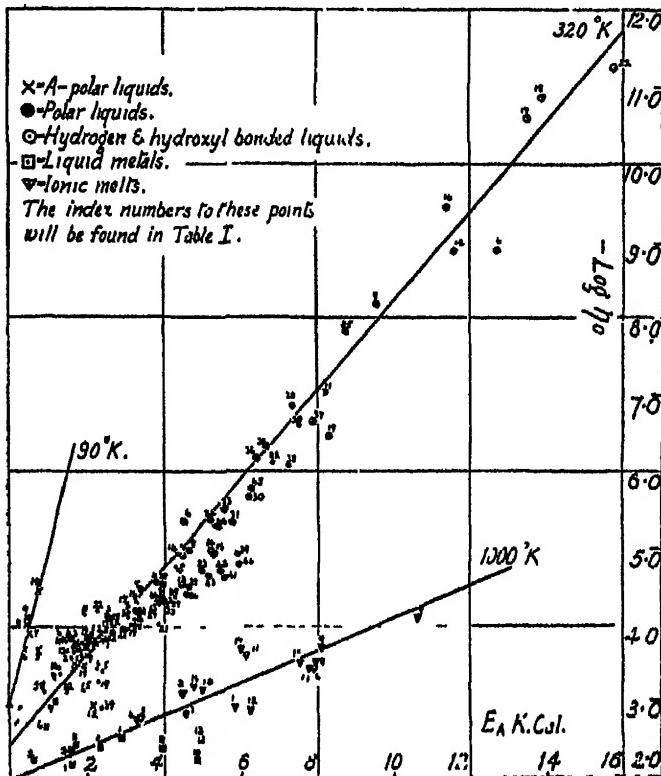


FIG. 5.— Log η_0 vs. E_A for fluids at different temperatures.

where V is approximately the volume of a unit of flow, and ΔS^* the entropy of activation. For the median curve of Fig. 6 one then has

$$\Delta S^* = \frac{0.77 E_A}{RT} - 4.60 \log 0.93 V \quad \quad (6)$$

This equation supports the prediction (p. 49) that the entropy of activation is made up of two parts:

(1) A positive component depending directly on E_A , as required by the zone theory of viscous flow and given by the term $\frac{0.77 E_A}{RT}$.

(2) A negative component not depending primarily on E_A . According to the zone theory this component is the result of synchronisation between certain rotatory and vibratory inter-molecular movements necessary for a successful unit act of flow or diffusion. A number of kinds of co-operative movement may lead, within each activated zone, to a successful act of flow

while a range of zone sizes may contribute to flow.⁶ If one zone size dominates in its contribution the co-operative entropy is $\Delta S_c = R \ln \Sigma (1/m)^n$ where $(1/m)^n$ is the probability that each of n particles moves simultaneously in one of m preferred directions, and the n 's and m 's may alter among the terms in the summation, according to the type of co-operation. Thus, from ΔS_c one may calculate $\Sigma (1/m)^n$, the co-operative term. When E_A/T is small, the term $0.77E_A/T$ may be less important than this co-operative entropy term, and so ΔS^* assumes a small negative value (cf. ref. 12). If E_A/T is large, ΔS^* becomes positive and often considerable. Table II shows the subdivision of the observed entropy of activation ΔS^* into the two components - the entropy of zone loosening (ΔS_c^*) due

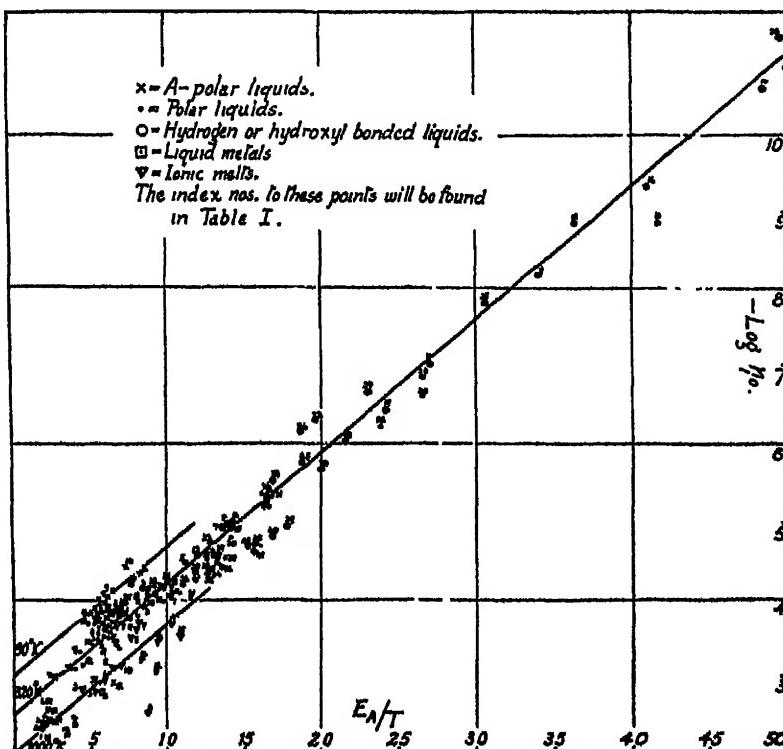


FIG. 6. — Log η_0 vs. E_A/T .

to absorption of the energy E_A , and the co-operative entropy (ΔS_c^*). In column 7 are given the co-operative factors corresponding to ΔS_c^* .

Discussion.

The present treatment of viscosity at first sight appears different from treatments¹⁴ assuming "holes" in the liquid as a preliminary to the unit act of flow. In fact, however, the zone theory includes such treatments by postulating the need for synchronised movements in such a way as to permit place changes. One suitable type of synchronisation is obviously hole formation, where each of n atoms momentarily draws away from a certain point leaving a gap where readjustments may occur. If there are m preferred directions of intermolecular vibration, the chance

¹⁴ E.g. ref. 8, p. 477, p. 486.

NON-POLYMERISED FLUIDS

of a hole being formed is then $(1/n)^n$ (see p. 56), and the term ΔS_c^* , or *entropy of co-operation* given in Table II becomes part of the *entropy of hole formation*. However synchronised movements may be possible which on absorption of the energy E_A culminate in a unit flow process without involving any actual hole, and the zone theory, recognising this, allows for any fruitful co-operative movements. It further emphasises the role of the activation energy in loosening a zone within which the unit flow process occurs—a role which if E_A is large is shown in this paper to dominate the process. One notes that ΔS_c^* in Table II, unlike ΔS_s^* , remains relatively constant. That is, the co-operative effect is similar for numerous liquids, as indeed is to be inferred from Fig. 6.

Copley¹⁵ observed relations between $\log \eta_0$ and E_A on plotting Ward's¹⁶ viscosity data. Curves for liquid permanent gases ($\sim 90^\circ\text{K}$) for polar liquids ($\sim 320^\circ\text{K}$) and for ionic melts ($\sim 1000^\circ\text{K}$) had different

TABLE II.—ENTROPY OF ZONE LOOSENING (ΔS_c^*) AND CO-OPERATIVE ENTROPY (ΔS_s^*) IN VISCOSITY FLOW.

Liquid.	Temp. Range (°)	E_A (Cal./Mol. of Unit Process),	ΔS^* (Cal./Mol./ Degree.)	ΔS_c^* (Cal./Mol./ Degree.)	ΔS_s^* (Cal./Mol./ Degree.)	The Co-opera- tive Factor $\Sigma(1/n)^n$.
Glycol	20	11,720	19.6	33.4	- 19.8	10^{-3}
Ether ‡	20	1,910	- 5.0	5.0	- 10.0	6.7×10^{-3}
Mercury	20	545	- 6.8	1.4	- 7.6	2.2×10^{-1}
Water	30-70	3,380	4.0	8.0	- 4.0	1.4×10^{-1}
Methyl alcohol	30-70	2,060	- 1.1	4.0	- 6.0	5×10^{-2}
Ethyl alcohol	30-70	3,440	1.4	8.1	- 6.7	3.5×10^{-2}
n-Propyl alcohol	30-70	4,080	1.9	9.6	- 7.7	3.2×10^{-2}
iso-Propyl alcohol	30-70	5,060	5.1	21.9	- 10.8	3.3×10^{-2}
n-Butyl alcohol	30-70	4,680	1.0	11.0	- 8.0	1.6×10^{-2}
iso-Butyl alcohol	30-70	5,740	0.0	13.5	- 7.5	2.3×10^{-2}
n-Pentane	30-70	1,670	- 5.8	3.9	- 10.7	3.5×10^{-2}
iso-Pentane	30-70	1,530	3.0	3.6	- 7.0	2.2×10^{-2}
n-Hexane	30-70	1,790	- 2.3	4.2	6.4	4.0×10^{-2}
n-Octane	30-70	1,860	- 4.6	4.2	8.8	1.2×10^{-2}
Ethyl bromide	30-70	1,930	- 2.4	4.8	- 7.2	2.7×10^{-2}
Ethyl iodide	30-70	1,900	4.4	10.1	11.1	1.55×10^{-2}
n-Butyl bromide	30-70	1,950	- 4.8	4.0	- 8.8	1.2×10^{-2}
Aretone ‡	7.0-17.0	1,700	5.2	4.8	0.4	0 $\times 10^{-2}$
Carbon disulphide	30-70	1,070	4.4	12.8	2.0	1.1×10^{-2}
Phenyl chloride	30-70	1,790	4.2	4.2	11.4	1.4×10^{-2}
Phenyl bromide	30-70	1,960	4.6	4.6	0.4	10^{-2}

slopes but apparently a common origin. Ward's data, however, require some arithmetical correction, and the corrected data are all included in Fig. 5. The best median lines do not have a common origin. Moreover, the differences in slope are not due, as suggested, to differences in chemical type, but to the different temperature ranges involved. Thus liquid metals and ionic melts, examined at similar temperatures, give points distributed about a median— $\log \eta_0$ vs. E_A line (Fig. 5) appropriate to the mean temperature, irrespective of whether metal or ionic melt is involved. Similarly, a-polar liquids examined in the range $0-100^\circ\text{C}$. belong to the same median line (which is appropriate to $\sim 50^\circ\text{C}$) as do

‡ The value of E_A for ether and acetone are taken from Table I (ii). The values given by Stearn and Ilyring¹⁸ appear to be low. Otherwise their data are used, which sometimes differ but not importantly from the calculations in this paper (Table I).

¹⁵ G. N. Copley, *Nature*, 1941, 147, 207.

polar or hydroxyl bonded liquids studied in the same range. On the other hand, points for any a-polar liquids examined at liquid air temperatures fall on a quite different curve.

No attempt is made here to discuss properties of functional relations between $\log D_0$ and E_A (from $D = D_0 e^{-E_A/RT}$), but attention has been drawn earlier to the existence of such relations, and to the continuity between liquids and rubber-like polymers as diffusion media.⁹ Both properties are predicted by the zone theory.

Summary.

The Arrhenius equation ($\eta \cdot \eta_0 e^{-E_A/RT}$) has been used in a study of the viscosity of many pure liquids of all kinds. In some E_A varies with temperature, in others it is nearly independent of temperature. Variations of E_A with the nature of the liquid; and of E_A and $-\log \eta_0$ with chain length in some homologous series are discussed in terms of current views on the liquid state.

Consistent functional relations are found between $-\log \eta_0$ and E_A . These appear as straight lines of slopes and intercepts on the $-\log \eta_0$ axis increasing as temperature decreases. The same consistent behaviour is noted when $-\log \eta_0$ is plotted against E_A/T . These relations are independent of the nature of the liquid for liquid permanent gases, a-polar liquids, polar liquids, hydrogen and hydroxyl bonded liquids, non-polymerised ionic melts and liquid metals. The data approximate to the general viscosity function $\sim 3.71 \times 10^{-2} e^{0.22E_A/RT}$ poises.

The zone theory of viscous flow gives a satisfactory interpretation of, or predicts, the various properties observed above.

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THE VISCOSITY OF PURE LIQUIDS.

II. POLYMERISED IONIC MELTS.

By R. M. BARRER.

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The glasses and polymerised ionic melts constitute a group of fluids of major importance, which as the sequel indicates show certain differences from previously considered liquids of Pt. I, although behaving consistently as a class. All liquids in this category are characterised by high viscosity, η , and a large Arrhenius energy of activation, E_A , ($\eta = \eta_0 e^{-E_A/RT}$). Considerable attention has already been paid to the influence of temperature and composition upon viscosity.¹⁻⁹

¹ H. R. Lillie, *J. Am. Cer. Soc.*, 1939, 22, 367.

² L. Jancke, *Z. physik. Chem., A*, 1939, 184, 309.

³ E. Soddon, *J. Soc. Glass Tech.*, 1939, 23, 36.

⁴ N. W. Taylor, *J. Am. Cer. Soc.*, 1939, 22, 1.

⁵ N. W. Taylor and R. F. Doran, *Glass. Ind.*, 1939, 20, 173; *ibid.*, 1941, 24, 103.

⁶ N. W. Taylor and P. Dear, *J. Am. Cer. Soc.*, 1937, 20, 296.

⁷ N. W. Taylor and McNamara and J. Sherman, *J. Soc. Glass Tech.*, 1937, 21, 61.

⁸ G. J. Bair, *J. Am. Cer. Soc.*, 1936, 19, 347.

⁹ M. Scobey, *Bull. Soc. Chim. Belg.*, 1938, 47, 889.

¹⁰ Thorpe's *Dictionary of Applied Chemistry*, Vol. V, 1941 edn., p. 541.

¹¹ *International Critical Tables*, Vol. VII, p. 212.

¹² M. Volarovich and A. Leontjeva, *J. Soc. Glass Tech.*, 1936, 20, 139, Sample I, third series.

The Data.

Typical data are presented in Table I, and Fig. 1 shows the relation between $-\log \eta_0$ and E_A/T , for a variety of such fluids. In this figure is given, in curve 1, the corresponding median line from ref. to, Pt. I, Fig. 6, for non-polymerised fluids at 320° K. The following behaviour is noted :

(1) There is a characteristic relationship between $\log \eta_0$ and E_A/T recalling that already observed for simple liquids (ref. to, Fig. 6). The new median line is considerably below that for simple liquids, which is reproduced for comparison in Fig. 1. It seems probable that the median line of Fig. 1, which covers the values of E_A/T from 8.6 to 262.7 and of $-\log \eta_0$ from 0.67 to 42.8, has a slight upward curvature.

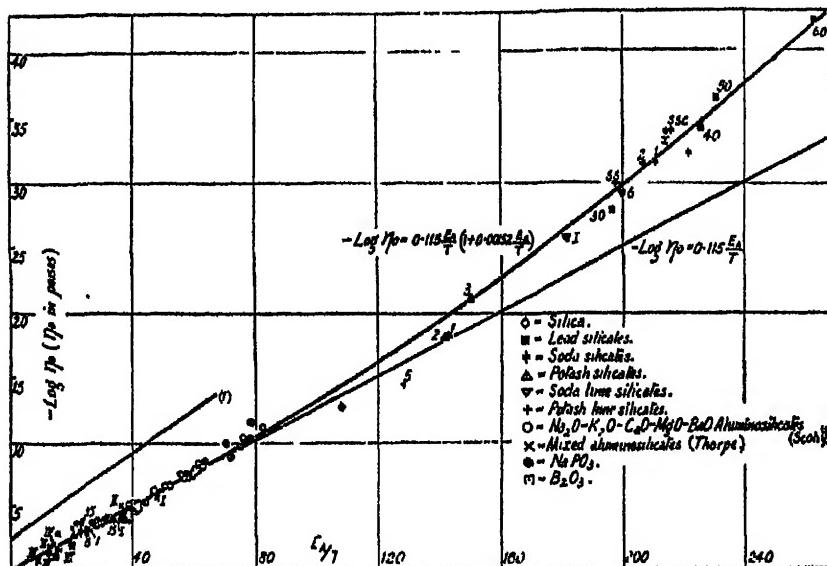


FIG. 1.— $-\log \eta_0$ vs. E_A/T for silicate and other glasses.
Curve (1) is the corresponding curve at 320° K. for molecular fluids.¹⁰ The data taken from Scully⁸ are not numbered.

(2) The median line for simple liquids lies above that for polymerised ionic melts, by amounts considerably more than the term $\log T_1/T_0$ of ref. ¹⁰, p. 46. The initial slopes are also slightly different. That the median line for glasses lies below that for simple liquids implies that for a successful unit flow process in glasses more complex phase relations between vibrations and rotations must be fulfilled. The initial smaller slope for liquid glasses indicates that for a given E_A/T the activated zone is less loosened than it is in non-polymerised fluids.

The median curve of Fig. 1 can be accurately represented by

$$-\log \eta_0 = 0.115 E_A/T (1 + 0.00152 E_A/T) \quad . \quad . \quad . \quad (1)$$

for $8.6 < E_A/T < 262.7$ (Table I). Over the range $8.6 < E_A/T < 100$ the curve is given without appreciable error by

$$-\log \eta_0 = 0.115 E_A/T. \quad . \quad . \quad . \quad . \quad (1a)$$

¹⁰ Barrer, *this journal*, preceding paper.

TABLE I.—VISCOSITY DATA FOR POLYMERISED IONIC MELTS.*

Glass.	$-\log \eta_0$	R_A (c.c./Avogadro Number of Unit Viscosity).	Temperature Range ($^{\circ}\text{C}.$).	R_A/T Mean.	f (Nearest Whole Number).	Total Energy per Degree of Freedom in the Activated State.	Reference.
I	3.28	54,700	750-1,000	47.7	9	8,340	11
I	4.05	55,000	1,000-1,300	35.9	7	10,200	11
II	3.06	51,200	1,000-1,300	35.9	7	10,200	11
IV	1.90	19,000	1,000-1,300	13.5	2 or 3	10,900	11
V	1.80	17,700	1,000-1,300	12.4	2	11,800	11
VI	1.70	16,700	1,000-1,300	12.5	3	9,700	11
III	1.28	17,200	1,100-1,200	12.1	2	11,400	11
III	0.67	13,100	1,200-1,300	8.6	2	9,400	11
B_2O_3	1.90	21,400	750-850	19.95	4	7,500	12
B_2O_5	1.23	17,800	850-1,100	14.30	3	8,400	13
NaPO_3	3.70	20,100	650-700	21.45	4	7,000	13
NaPO_4	2.90	16,700	800-850	15.17	3	7,700	13
Na lime silicate I	23.74	140,000	475-525	181.5	—	—	7
" " 6	20.33	155,000	471-530	199.5	—	—	5
Potash lime silicate 5	14.43	103,000	532-557	118	—	—	5
Potash silicate 1	18.15	106,000	450-494	142.4	—	—	5
" " 2	18.04	105,000	441-494	141.8	—	—	5
" " 3	20.41	110,000	425-494	140.7	—	—	5
SiO_2	12.53	177,500	1,200-1,440	108.3	20 or 21	12,740	13
Na silicate VII	34.99	159,000	480-470	221.7	—	—	7
" " 1	4.62	49,500	900-1,000	40.5	9	7,900	1
" " 1	3.10	40,000	1,300-1,400	24.7	5 or 6	10,500	1
" " 2	4.84	46,000	900-1,000	37.6	8 or 9	7,800	1
" " 2	2.93	37,500	1,300-1,400	29.1	5	10,700	1
" " 3	4.81	46,000	900-1,000	37.6	8 or 9	7,800	1
" " 3	2.97	37,500	1,300-1,400	29.1	5	10,700	1
" " 4	4.34	47,400	900-1,000	37.6	8 or 9	7,800	1
" " 4	3.00	37,500	1,300-1,400	29.1	5	10,700	1
" " 5	4.61	47,400	900-1,000	38.8	8 or 9	8,000	1
" " 5	3.01	37,500	1,300-1,400	23.1	5	10,700	1
" " 6	4.34	45,300	900-1,000	37.1	8	8,100	1
" " 6	3.43	40,000	1,300-1,400	24.7	5 or 6	10,400	1
" " 9	4.02	45,900	900-1,000	34.3	7 or 8	8,300	1
" " 9	3.83	37,500	1,300-1,400	23.1	5	10,700	1
" " 15	4.31	41,200	900-1,000	33.7	7 or 8	7,900	1
" " 15	3.68	37,500	1,300-1,400	23.1	5	10,700	1
" " 20	34.18	136,000	444-471.2	216	—	—	6
" " x	33.64	135,500	442-471.5	215	—	—	6
" " No. 2	31.63	130,000	427.9-471.0	207	—	—	6
" " ss	30.0	125,000	435.0-469.8	198	—	—	6
" " No. 1	31.75	133,800	427.8-471.0	212	—	—	6
Lead silicate No. 30	47.9	146,500	430-524	196.5	—	—	8
" " No. 40	34.4	128,300	400-454	225.8	—	—	8
" " No. 50	36.8	133,500	361-425	230.5	—	—	8
" " No. 60	42.8	163,900	332-370	262.7	—	—	8

* The extensive data of Scohy⁸ may be added to this Table, but owing to their number, and availability in suitable form elsewhere, they are not included here. Analyses of the different glasses referred to in Table I are given in the original references.

Thus the mean viscosity function for the glasses of Table I and those listed by Scohy,⁶ covering numerous reliable data, is

$$\eta = e^{0.47 E_A/RT} \cdot 0.0016(E_A/RT)^2 \text{ poises } (8.6 + E_A/T) .$$

$$(9) \quad \eta = e^{0.47 E_A/RT} \text{ poises } (8.6 + E_A/T \sim 100) .$$

Thus for any particular glass one may write

$$\eta = k e^{0.47 E_A/RT} \cdot 0.0016(E_A/RT)^2 \text{ poises.} .$$

where k is a constant introduced to allow for individual deviations from the mean curve. These equations may be compared with the corresponding equations of ref.¹⁰, p. 49.

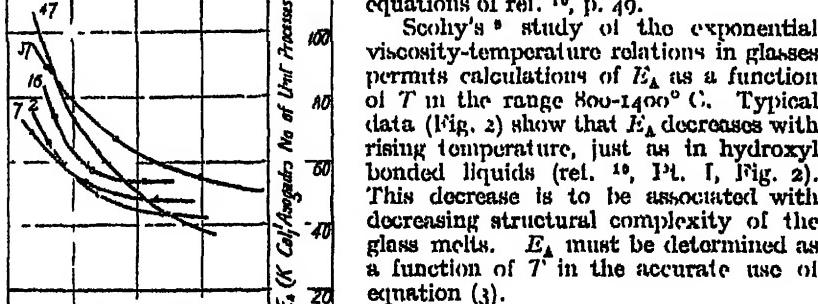


FIG. 2.—Variation of E_A with temperature for typical glasses, from data of Scohy.⁶ The numbers refer to the particular glass studied.

curve. It will now be shown that, subject to reasonable approximations, this is indeed true. The viscosity equation is

$$\phi = \frac{f}{\eta} = \frac{1}{kT} e^{-E/RT} \sum_{i=1}^n \frac{\rho_i \lambda_i b}{d \tau_0} \left(\frac{E}{RT} \right)^{i-1} (i-1)! . \quad (4)$$

Here ϕ denotes the fluidity, ρ_i is the co-operative factor, of ref.¹⁰ (there being a different and appropriate ρ_i for each term in the summation), $E = E_A + fRT$ is the total energy per Avogadro number of activated degrees of freedom, λ_i and d are distances of molecular magnitudes, τ_0 is the mean period of oscillation of librating groups or molecules within the activated zone, b is a quantity having the dimensions of a volume,* and f denotes the number of degrees of freedom in the activated zone. Re-writing (4) and using the expression $\phi = \phi_0 e^{-E_A/RT}$ gives

$$\ln \phi_0 = -\ln \eta_0 = \ln k + \ln \left[\sum \left(\frac{E_A}{RT} + f \right)^{i-1} \frac{\rho_i}{(i-1)!} \right] - f . \quad (5)$$

where $k = \frac{\lambda_i b}{2d\tau_0} \cdot \frac{1}{kT}$. By employing the full expression of Stirling's theorem,[†] one may expand the factorial in (5). If also the summation

* For a derivation of this equation see ref.¹⁰.

† The approximation used is valid for all values of f , from unity upwards.

¹⁰ Barrer, *Trans. Faraday Soc.*, 1942, 38, 322.

may be replaced by a single dominant term * (cf. Fowler and Guggenheim¹⁴) one obtains

$$\ln \phi_0 = [\ln k - \frac{1}{2} \ln 2\pi - 1] + \ln p_f - (f - \frac{1}{2}) \ln (f - 1) \\ + (f - 1) \ln f + (f - 1) \ln \left(\frac{E_A}{f R T} + 1 \right) . \quad (6)$$

Trial shows that the terms $(f - \frac{1}{2}) \ln (f - 1)$ and $(f - 1) \ln f$ have but slightly differing values for reasonable values of f , and since their signs are opposite they nearly cancel, contributing little to the observed large range in $-\ln \eta_0$, and so

$$\ln \phi_0 = -\ln \eta_0 - \ln k_1 + \ln p_f + (f - 1) \ln \left(\frac{E_A}{f R T} + 1 \right) . \quad (7)$$

where $\ln k_1 = [\ln k - \frac{1}{2} \ln 2\pi - 1]$. The simplest expression of previse (1) of the zone theory (ref. ¹⁰, p. 40) is that $\beta E_A / R T = f$, where β is a constant. Accordingly,

$$\ln \phi_0 = \ln k_1 + \ln p_f + \left(\frac{\beta E_A}{R T} - 1 \right) \ln \left(\frac{\beta + 1}{\beta} \right) (8)$$

It is apparent that equation (8) has the observed linear form of the $-\log \eta_0$ vs. E_A/T curves of Fig. 6, ref. ¹⁰, in which $1.85 < E_A/T < 50$. Similarly for glasses, Fig. 1 of this paper shows a nearly straight line for the range $8.6 < E_A/T < 100$ of Table I, and deviations from it are still slight over a greater range in E_A/T . Deviations from a straight line in the sense of Fig. 1 would be anticipated from equation (8) either if $\ln p_f$ increased appreciably for very large values of E_A/T , or if, as also seems likely, a number of terms in p_f and f (eq. 7) contribute to flow when the zone is large.

Values of η_0 .

In Table I the extreme values of η_0 are 2.14×10^{-1} and 1.58×10^{-43} poises. This remarkable range must be explained in a reasonable manner by an adequate theory of viscous flow. The transition state method interprets such a range in terms of a variable entropy of activation. It does not of itself give any physical picture of the origin of this entropy. Attempts to extend ^{8, 15} Frenkel's treatment¹⁶ of simple liquids to polymerised ionic melts have through misapplication led to impossible results.[†] The present view is that the positive part of the entropy of activation \ddagger arises from a loosening of the fluid within the zone due to absorption of energy in all the degrees of freedom constituting the zone. The number of these degrees of freedom may be considerable. The entropy increase may be large if E_A and zone size are large, or small if E_A and zone size are small. Moreover, equations (8) or (7) of the previous

¹⁴ Fowler and Guggenheim, *Statistical Thermodynamics*, C.U.P., 1930, p. 498.

¹⁵ R. Preston and E. Seddon, *J. Soc. Glass Tech.*, 1937, 21, 123.

¹⁶ J. Frenkel, *Z. Physik*, 1926, 35, 652.

* This requires that the value of one term $\left(\frac{E_A}{R T} \right)^{f-1} \frac{1}{(f-1)} p_f$ should be much greater than that of any other term in the summation. It is likely that a limited spectrum of these terms in equation (6) would be a physically more correct, although mathematically less tractable, approximation, especially for large zones.

† The view developed was that the range in η_0 is a measure of the range of "cluster sizes" or sizes of units participating in each unit act of flow. If at one end of the scale the cluster size were 10^{-43} c.c., at the other it would become 10^{40} c.c. Moreover, even in the largest such cluster the energy of activation is still assumed concentrated in a single degree of freedom, having a probable volume of $\sim 10^{-45}$ c.c..

‡ There is a negative part, resulting from the term p_f of equation (4) (see ref. ¹⁰, Table II, and p. 56).

POLYMERISED IONIC MELTS

section for a reasonable choice of β or of f respectively, and using the experimental values of E_A/T will easily cover the extremes in η_0 , without leading to any physically unacceptable zone size in the unit process of flow. It is emphasised that the activated zone itself is not regarded as moving, but that within the zone its components undergo a reorganisation amounting to a release of strain, i.e. a shear, under the forces producing viscous flow.

Degrees of Freedom Involved in Flow.

In a previous section premise (1) of the zone theory was expressed as $\beta E_A/RT = f$, and from equations (1a) and (8) it can be shown that for numerous glasses $\beta = 0.44$. One may accordingly calculate f , the number of activated degrees of freedom involved in each zone in the act of flow.* These values of f are given in column 6 of Table I for those glasses for which equation (1a) is a reasonable approximation. The same method may be applied to molecular fluids. Thus the equation of the median line of Fig. 6, ref. ¹⁰, is $-\log \eta_0 = 2.43 + 0.167 E_A/T$ whence β in equation (8) is 1.45. Then from $\beta E_A/RT = f$ one finds the following extreme ranges in f for the liquids of Table I, ref. ¹⁰:

A-polar liquids $f = 3$ to 7.

Polar, hydrogen and hydroxyl bonded liquids $f = 3$ (for ether) to 37 (for *p*-cresol).

Liquid metals $f = 1$ to 3.

Simple ionic melts $f = 4$ to 8.

Table II gives details of these and other data for simple ionic melts, to be compared with the corresponding data for polymerised ionic melts in Table I.

TABLE II.—TOTAL ENERGY PER DEGREE OF FREEDOM IN THE ACTIVATED STATE IN SIMPLE IONIC LIQUIDS.

Liquid.	E_A (Cal./Avogadro Number of Unit Processes).	f (Nearest Whole Number).	Total Energy E (Cal./Avogadro Number of Activated Degrees of Freedom).
NaCl	9,400	4 or 6	4,030
NaBr	10,630	7 or 8	3,490
NaNO ₃	3,410	4	2,110
NaOH	5,470	5 or 6	2,420
KCl	7,830	5	3,930
KBr	7,960	5 or 6	3,400
KNO ₃	4,470	5	2,280
KOH	6,230	5 or 6	3,350
K ₂ Cr ₂ O ₇	6,740	7	2,400
AgBr	5,420	4	3,180
AgI	5,810	4	3,410
AgNO ₃	5,230	4	2,930
PbCl ₂	7,780	8	2,600
PbBr ₂	7,570	7	2,480
BaCl ₂	4,960	6	2,060
LiNO ₃	5,970	8	2,810

The Total Energy per Activated Degree of Freedom.

If from the observed energy of activation E_A , one may now calculate the average total energy in each activated degree of freedom in the zone. These energies, which are given in column 7 of Table I (glasses) and in column 3 of Table II (simple ionic melts), show that the structural stability in simple ionic liquids, while considerable, is much less than in liquid glasses.

Finally, in Table III, analogous data taken from ref. ¹⁰ are presented for typical molecular and atomic fluids. The energy, E ,

* This calculation is naturally subject to the approximations involved in eq. (8).

gives a measure of the total energy needed to cause structural breakdown and readjustment of various types of bond in liquids. It is then parallel with the bond strengths in the liquid.

TABLE III.—TOTAL ENERGY PER DEGREE OF FREEDOM IN THE ACTIVATED STATE OF TYPICAL MOLECULAR AND ATOMIC LIQUIDS.

Liquid.	Nature of Bond.	E_A (Cal./Avogadro Number of Unit Processes).	f (Nearest Whole Number).	Total Energy E (Cal./Avogadro Number of Activated Degrees of Freedom).
Argon .	Van der Waals	5.4	4	100
Methane .		740	5 or 6	333
n-Octane .		2,185	5	1,100
CCl ₄ .		2,700	7	1,600
Mercury .	Metallic	508	1 or 2	1,040
Silver .		4,870	3	4,400
Lead .		2,320	2	2,880
Sulphur dioxide	Dipole-dipole and van der Waals	1,300	4	840
Acetone .		1,850	5 or 6	700
Quinoline .		3,970	9 or 10	1,010
Benzyl benzoate		7,500	19	900
Stannic chloride		1,475	3 or 4	1,070
Water .	Hydrogen or hydroxyl bond and van der Waals	4,530	12	940
Sulphuric acid		5,940	13	1,180
t-Butyl alcohol		9,560	25	1,000
Bromal hydrate		15,770	36	1,070
p-Cresol .		23,900	37	930
Acetic acid .		2,130	5	1,130

Discussion.

The size of the activated zone is measured by the number of degrees of freedom contained in it. In the case of many glasses, and of polar and hydroxyl bonded liquids, the zone size becomes considerable, and if one associates a volume of $\sim 3 \times 10^{-22}$ c.c. with each such degree of freedom, the zone volume per Avogadro number of zones ranges from 18 c.c. (Hg) to 666 c.c. for p-cresol, and is probably even greater for some of the glasses of Table I with very large values of E_A/T . The units comprising the zone, and which are involved in the internal reorganisation or shear in each zone, may be molecules, atoms, ions, or groups such as SiO₄⁴⁻ or —CH₂—, according to the nature of the liquid. The idea of a definite segment¹⁶ of a long chain molecule as a participating unit remains, but the zone is likely to be composed of a number of small interlacing segments, rather than the single, semi-isolated, and very large segment of Eyring.

Fig. 3 compares the Arrhenius energies of activation now available for numerous rate processes. The greatest range at present appears in viscous flow (550 cal. (liquid Hg) < E_A < 191,000 cal. (SiO₂, glass)). There is a scarcity of data for flow of organic polymer systems, where E_A takes values from 10,000 cal. for rubber to 26,000-41,000 cal. for pitches.* These ranges are frequently only limited by the experimental techniques available or by the paucity of data. It is characteristic of

* Calculated from data of Mack.¹⁷

¹⁷ J. Soc. Chem. Ind., 1939, 58, 306.

reaction kinetics and of diffusion in *crystalline* solids that E_A is not normally sensitive to temperature. On the other hand, processes occurring in condensed phases and involving activated zones of considerable size frequently show that E_A is sharply dependent on temperature (ref. 1, Fig. 2, and Fig. 2 this paper). Since ΔH^\ddagger and E_A , the heat and Arrhenius energy of activation respectively, are simply related, and since

$$\Delta H^* = \Delta H_0^* + \int_0^T \Delta C_p dT$$

Arrhenius Energy of Activation in Kilocalories per Avogadro Number of Unit Processes.

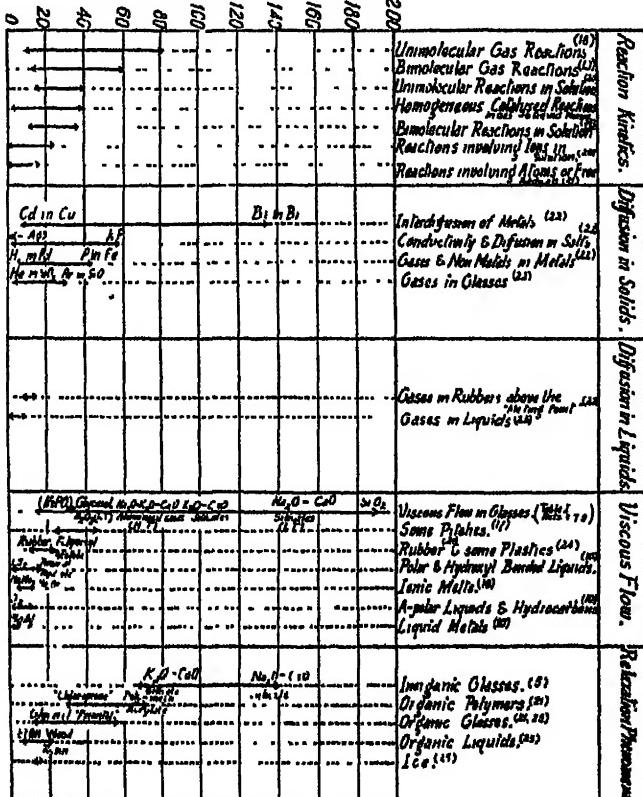


FIG. 3.—Comparison of energies of activation of typical rate processes.

(where ΔH_a^* is the heat of activation at 0° K.) such effects are logically to be ascribed to large changes in specific heat (ΔC_p^*) between activated and normal states, which in turn are compatible with loosening or breakdown of complex structures on activation.

¹⁸ P. Fugassi and E. Warrick, *J. Physic. Chem.*, 1942, 46, 630.

¹⁹ C. N. Hinshelwood, *Kinetics of Chemical Reactions*, O.U.P., 1933 ed.

²⁰ E. Moelwyn-Hughes, *Kinetics of Reactions in Solution*, O.U.P., 1933.

¹¹ Cf. Glasstone, Laidler and Eyring, *Theory of Rate Processes*, McGraw-Hill.

ok Co., 1941.

²² R. M. Barrer, *Diffusion in and through Solids*, C.U.P., 1941.

²⁵ R. M. Barrer, *Trans. Faraday Soc.*, 1939, 35, 644.

²⁴ E.g. R. F. Tuckett, *Ibid.*, 1942, 38, 330.

²² Advances in Colloid Science, Vol. I, 1942, p. 320, Interscience Publishers.

Summary.

The Arrhenius energy of activation, E_A , for polymerised ionic melts may be very large and frequently depends on temperature. A relation was found between $-\log \eta_0$ and E_A/T which obeys the equation

$$-\log \eta_0 = 0.115 E_A/T (1 + 0.00152 E_A/T).$$

Over the range $8.6 < E_A/T < 100$ the relation is virtually a linear one, but the straight line has a different slope and intercept from that for molecular and non-polymerised fluids. Reasons based on the zone theory are given for the relative position and slope of these lines.

The linear form of the $-\log \eta_0$ vs. E_A/T curve was derived, and similarly it was shown that the zone theory could reasonably cover the observed range of values of η_0 of from 2.14×10^{-1} to 1.6×10^{-41} poises.

In many flow systems it was possible to estimate the number of degrees of freedom involved in each zone, and the total energy per activated degree of freedom necessary for flow to occur, as well as the zone volume. This calculation was carried out for typical glasses, liquid metals, simple ionic melts, a-polar and polar or hydroxyl bonded fluids.

The range of the Arrhenius energy of activation was compared for many kinds of rate processes.

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THE SALT ERROR OF THE QUINHYDRONE ELECTRODE IN AQUEOUS NITRIC ACID, AND THE POTENTIALS OF THE HYDRO-QUINHYDRONE AND QUINO-QUINHYDRONE ELECTRODES.

By H. I. STONEHILL.

Received 29th August, 1942.

In connection with other work in progress, it was required to know the quinhydrone electrode salt error in aqueous solutions of nitric acid at 25° C. Hovorka and Dearing¹ determined this salt error in aqueous solutions of various sulphates, chlorides, the corresponding free acids, and some non-electrolytes, by measuring the E.M.F. of cells of the type



They showed that the salt error was proportional to the concentration of added solute up to about 1 N., and that it was additive for mixtures of two solutes in some cases but not in others.

It is clear that this cell cannot be used for solutions of nitrates, since, especially in acid solution, the nitrate ion is rapidly reduced at the hydrogen electrode, which becomes erratic and irreversible. It is therefore surprising that von Kiss and Urmanczy² claim to have determined the quinhydrone

¹ Hovorka and Dearing, *J.A.C.S.*, 1935, 57, 446.

² Von Kiss and Urmanczy, *Z. physik. Chem.*, A, 1934, 169, 37.

68 THE SALT ERROR OF THE QUINHYDRONE ELECTRODE

electrode salt error in 0.5 and 1.0 N. solutions of potassium and sodium nitrates at 25° C. by measuring the E.M.F. of the cells

Au | 0.05 N. HCl, nitrate, quinhydrone (sat.) | 0.05 N. HCl, nitrate | H₂, Pt
and

Au | 0.01 N. HCl, nitrate, quinhydrone (sat.) | KCl (sat.) | KCl (sat.),
Hg₂Cl₂ (sat.) | Hg | Hg₂Cl₂ (sat.), KCl (sat.) | KCl (sat.) | 0.01 N.
HCl, nitrate | H₂, Pt,

obtaining $\Delta E_{\text{NANO}_3} = -0.0000 - 0.00414 I$, $\Delta E_{\text{KNO}_3} = -0.0007 - 0.00366 I$, where ΔE denotes the salt error in volts, and I the ionic strength of the solution. They state that the cells equilibrated within 20 min., and then remained constant within 0.001 v. for 20 min., although they note deviations from the linear law for ΔE due to the "störenden Wirkung" of NO₃⁻. In order to confirm that reliable results cannot be obtained from the hydrogen electrode in nitrate-containing solutions, some preliminary measurements were made in the author's laboratory of the E.M.F. at 25° C. of the cell

Pt and Au | quinhydrone (sat.), 0.05 N. HCl, 0.1 N. KNO₃,
| 0.05 N. HCl, 0.1 N. KNO₃, | H₂, Pt.

It was found, as expected, that no constant E.M.F. was obtained at all, the value rising rapidly for several hours; some of the solution removed from the hydrogen electrode compartment, upon addition of acidified potassium iodide and chloroform, coloured the latter violet, indicating reduction products.

It is essential, in determining the quinhydrone electrode salt error, to compare this electrode with another hydrogen-ion reversible electrode having no salt error. Both the hydro-quinhydrone and the quino-quinhydrone electrodes meet this requirement,^{3, 4} and hence a direct determination of the salt error in nitric acid was made by measuring the E.M.F. of the cells

(a) Pt or Au | quinhydrone (sat.), HNO₃ (*c* mol./l.) | HNO₃ (*c*),
quinhydrone (sat.), hydroquinone (sat.) | Pt or Au

and

(b) Pt or Au | quinhydrone (sat.), HNO₃ (*c*) | HNO₃ (*c*),
quinhydrone (sat.), quinone (sat.), | Pt or Au.

Since the *pH* of 0.005 N. HCl with added potassium nitrate up to 1.0 N. is well within the range 2-8 over which the glass electrode is known to have no salt error,⁵ the E.M.F. of cells

(c) Pt | quinhydrone (sat.), 2 N. HCl | glass | 0.005 N. HCl,
KNO₃ (*c*), quinhydrone (sat.) | Pt

was measured in order to determine rapidly the quinhydrone electrode salt error in potassium nitrate solutions, and thence, assuming the additivity of salt errors, obtain a confirmatory value for the nitric acid salt error.

Experimental.

Approximately 2 N. stock solutions were prepared from B.D.H. Analar HNO₃ and HCl, and were diluted by volume as required. The HCl was standardised gravimetrically with Analar AgNO₃, and the HNO₃ volumetrically against the HCl acid *via* Na₂CO₃. KNO₃ and KCl (Analar) were dried in an electric oven at 130° C. Quinhydrone

³ Biilmann and Lund, *Ann. Chim.*, 1921, 16, 327.

⁴ S. P. L. Sørensen, M. Sørensen and Linderström-Lang, *Ibid.*, 1921, 16, 283.

⁵ MacInnes and Balcher, *J.A.C.S.*, 1931, 53, 3375.

(Analar) was recrystallised from conductivity water at 60° C. and dried over CaCl₂. It produced an E.M.F. of 0.69904 v. in the cell



at 25° C. as compared with 0.69906 v. from Novorka and Dearing's best specimen,¹ while the unrecrystallised material gave a value 0.00042 v. lower. Commercial pure hydroquinone was recrystallised four times from conductivity water, and dried over CaCl₂ in air; slight oxidation to specks of quinhydrone occurred during drying, but this is obviously immaterial for present purposes. Quinone was prepared by oxidising some of the original hydroquinone with CrO₃ in ice-cold glacial acetic acid according to the method of Craven and Duncan;² the product was water-washed, dried in air, recrystallised twice from purified petroleum ether, b.p. 90°–100° C., and stored over paraffin wax *in vacuo*. Oxygen-free nitrogen and conductivity water (sp. conductivity about 0.6×10^{-6} mhos.), which was used for making all the solutions, were prepared as described elsewhere.³ Cylinder hydrogen was passed over a 25 cm. palladium wire electrically heated to dull redness, to remove oxygen, and then through a KOH wash-bottle.

The Pyrex glass cell (Fig. 1) consisted of an inner and an outer electrode compartment with a ground glass cap as junction between them. Each compartment contained two thick (20 S.W.G.) wire electrodes, one platinum, the other gold, which were welded to thin platinum wire sealed into the bottoms of mercury-filled glass tubes held in the pierced rubber stoppers closing the tops of the compartments. The inner compartment was also provided with a gas inlet tube and bubbler-trap gas outlet. The cell was cleaned in hot chromic-sulphuric acid, rinsed with tap water, distilled water and conductivity water in turn, and dried in an electric oven before each measurement. The electrodes were similarly cleaned and rinsed, then finally rinsed with appropriate cell solution. For the salt error measurements both compartments and the bubbler-trap were filled with a given acid solution, taking care to wet the ground cap surfaces with the latter before screwing them hard together; a slight excess of quinhydrone was placed in each compartment, the electrodes, etc., were assembled in position, the cell was placed in the thermostat, and purified nitrogen, previously passed through a saturator filled with cell solution and immersed in the thermostat, was bubbled through slowly for $\frac{1}{2}$ hour. Then the rubber stopper assembly was momentarily removed from the inner compartment, an excess of either quinone or hydroquinone was rapidly introduced, the stopper assembly replaced, and nitrogen passed for a further $\frac{1}{2}$ hour, whereupon the gas outlet was closed with a small rubber stopper and the nitrogen supply turned off. The nitrogen served the double purpose of stirring to accelerate saturation with quinone or hydroquinone, and removing oxygen, which rapidly attacks both of these in solution.*

* Craven and Duncan, *J.C.S.*, 1925, 127, 1489.

¹ Stonehill, *Trans. Faraday Soc.*, 1938, 34, 533.

* The quinhydrone electrode in nitric acid has been found by the author to give fairly steady potentials over several hours. With the addition of either quinone or hydroquinone, however, the electrode potential drifts appreciably. In the case of added hydroquinone this may obviously be ascribed to oxidation by HNO₃ or dissolved oxygen if the latter were present. It seems to the author that a similar explanation may apply to the quinone (*cf.* Beilstein's *Handbuch der Org. Chem.*, 1925, 7, 611, which reports the oxidation of quinone by nitric acid and by air). It is apparently not widely known that aqueous solutions of

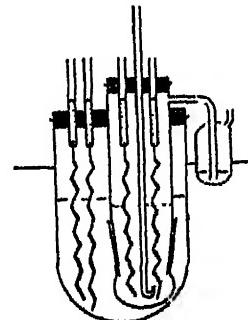


FIG. 1.

For the preliminary hydrogen electrode measurements the cell was slightly modified. The inner compartment electrodes were half-immersed 1 cm. squares of platinum foil, thinly platinised from a solution of platinic chloride in pure HCl; they were freed from chlorine by electrolysing dilute H_2SO_4 between them in pairs, with frequent reversals of current, were kept in distilled water when not in use, and were rejected unless they agreed in pairs within 0.00002 v. The same solution was placed in both electrode compartments, except that excess quinhydrone was added to the outer compartment only. Nitrogen was replaced by purified hydrogen, passing constantly at one bubble per second.

E.M.F. measurements were made to within 0.0001 v. for the salt error cells, and 0.00002 v. for the hydrogen electrode cells, using a Tinsley potentiometer and duplicate Weston cadmium cells recently certified by the N.P.L. The observed E.M.F. of the nitric acid salt error cells, after an initial period of 15-20 minutes for saturation of quinone or hydroquinone, increased (algebraically) steadily at the rate of about 0.1-0.4 mv. per hour. This is probably due to attack of the (hydro)quinone by nitric acid,* and was more pronounced the higher the acid concentration. It was eliminated by extrapolating the almost linear plots of E.M.F. *vs.* time to zero time after addition of (hydro)quinone. Both gold and platinum electrodes gave essentially the same extrapolated results, but the platinum electrodes in the presence of (hydro)quinone altered in potential more rapidly than the gold, in the more concentrated solutions. With quinhydrone alone as saturating solute, as in the outer compartment, both platinum and gold electrodes functioned equally well, with no significant drift.

Glass electrode measurements were made to within 0.0001 v. by means of a Cambridge valve electrometer. The Haber bulb type Corning 015 glass electrode contained a bright platinum wire dipping into 2 N. HCl saturated with quinhydrone. Three wide Pyrex tubes, similar to the outer vessel of Fig. 1, containing 0.005 N. HCl saturated with quinhydrone and respectively zero, approx. 0.5 N., and N. concentrations of added KNO_3 or KCl, were each provided with a bright platinum wire electrode and placed in the thermostat; after 20 minutes, the glass electrode, previously rinsed with appropriate solution, was introduced into each tube in turn, and the E.M.F. read after allowing 5-10 minutes for temperature equilibration each time. Body capacity and stray field effects were absent, and drift errors were negligible, as shown by the reproducibility of E.M.F. differences from one solution to the next.

The kerosene-filled thermostat was electrically heated and controlled by a mercury-toluene thermoregulator at 25 \pm 0.01° C., the temperature being set by a N.P.L. certified thermometer. The weights and volumetric apparatus employed were calibrated, and weighings were reduced to vacuum.

Results.

Table I gives the E.M.F.s of cells (a) and (b) for various HNO_3 concentrations c . The European sign convention is used throughout this

TABLE I.—E.M.F. (IN VOLTS) OF CELLS (a) AND (b) WITH NITRIC ACID.

c (mol./l.):

1.036	0.7784	0.5189	0.2077	0.1038	0.05197	0
E.M.F. of cell (a):						
0.0799	0.0809	0.0823	0.0843	0.0847	0.0850	(0.0852)
E.M.F. of cell (b):						
-0.0517	-0.0506	-0.0492	-0.0476	-0.0471	-0.0469	(-0.0465)

quinone are fairly readily oxidised in contact with air to a brown-black substance which may be easily obtained in quantity by attempting to recrystallise quinone from water in contact with air.

paper, i.e. an E.M.F. is positive if positive electricity tends to pass spontaneously from right to left through the cell as written.

These values give essentially linear plots of E.M.F. vs. c , and the method of least squares leads to the following equations for these lines :—

$$\text{for cell (a)} \quad E_a^{\text{HNO}_3} = 0.0852_5 - 0.0053_1 c \text{ volt},$$

$$\text{for cell (b)} \quad E_b^{\text{HNO}_3} = -0.0465_5 - 0.0052_1 c \text{ volt}.$$

The average salt error in nitric acid is thus $\Delta E_{\text{HNO}_3} = -0.0052_0 c$ volt.

To confirm that the method was reliable, similar measurements were made with HCl. Those are given in Table II, and also lead to linear plots

TABLE II. E.M.F. (IN VOLTS) OF CELLS (a) AND (b) WITH HYDROCHLORIC ACID.

c (mol./l.)	1.055	0.5275	0.1055	0
E.M.F. of cell (a)	0.0810	0.0835	0.0840	(0.0853 ₀)
E.M.F. of cell (b)	-0.0501	0.0483	-0.0468	(-0.0465 ₀)

of E.M.F. vs. c , the equations to which are found by the method of least squares to be

$$E_a^{\text{HCl}} = 0.0853_5 - 0.0034_8 c \text{ volt},$$

$$E_b^{\text{HCl}} = -0.0465_5 - 0.0033_1 c \text{ volt}.$$

Thus for $c = 0$ the E.M.F.s are practically the same as obtained from the nitric acid results, and further, the average salt error in hydrochloric acid is $\Delta E_{\text{HCl}} = -0.0034_8 c$ volt, as compared with Hovorka and Dearing's value, $-0.0036_1 c$ volt.¹ Since the present results with HCl were not so reliable as those with HNO_3 owing to the far more pronounced and rapid attack on quinhydrone and more especially quinone to form chloro-hydroquinone (*cf.* Hovorka and Dearing, *loc. cit.*), this is a satisfactory agreement.

Cells (c) with KNO_3 concentrations 0, 0.4996 and 1.000 N. gave the E.M.F. differences

$E_{0.0} - E_{0.5} = 0.0019$ v., $E_{0.5} - E_{1.0} = 0.0018$ v., $E_{0.0} - E_{1.0} = -0.0038$ v., indicating that KNO_3 produced a salt error proportional to its normality, of average value $-0.0038 c$ volt. A similar series of cells with KCl at concentrations 0, 0.5020 and 1.003 N. gave E.M.F.s 0.0102, 0.0114 and 0.0124 volt respectively, indicating a salt error increasing linearly with concentration according to the equation $\Delta E_{\text{KCl}} = -0.0022 c$ volt, identical with Hovorka and Dearing's value,¹ and thus checking the reliability of this use of the glass electrode. Combining the above value for ΔE_{KNO_3} with Hovorka and Dearing's values for ΔE_{HCl} and ΔE_{KCl} and assuming the additivity of salt errors, we have

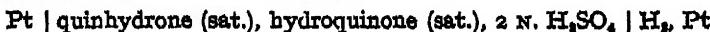
$$\Delta E_{\text{HNO}_3} = \Delta E_{\text{HCl}} + \Delta E_{\text{KNO}_3} - \Delta E_{\text{KCl}} \\ - c (-0.0036_5 - 0.0038 + 0.0022_0) = -0.0052 c \text{ volt},$$

which agrees well with previous value $-0.0052_0 c$ volt.

As a check on the additivity of salt errors, a cell of type (a) with 0.5 N. HCl plus 0.5 N. KNO_3 was measured. The E.M.F. was 0.0817 v., corresponding to a salt error of -0.0035_5 v., as compared with the value $-0.5 (0.0036_5 + 0.0038) = -0.0037$ v. calculated on the assumption of additivity. The agreement is satisfactory, in view of the previously mentioned disadvantage associated with HCl.

Assuming that the E.M.F.s of cells (a) and (b) at $c = 0$ are respectively 0.0852₅ v. and -0.0465_0 v., and combining with the standard potential 0.69938 v. of the quinhydrone electrode,¹ the values 0.6141₅ v. and 0.7458₅ v. are obtained for the standard potentials of the hydroquinhydrone and quino-quinhydrone electrodes respectively.

Schreiner⁸ found that for the cell



⁸ Schreiner, *Z. physik. Chem.*, 1925, 117, 57.

at 22° C., $E = 0.61496$ v., $dE/dT = -0.000641$ v./°C., giving at 25° C., $E = 0.6130$ v. Since there is no salt error, this is the standard potential of the hydro-quinhydrone electrode. Similarly, for the corresponding quino-quinhydrone cell, Schreiner found that $E = 0.77059 - 0.000842 t$ (v.) for $t = 5 - 15$ ° C. Assuming that the temperature coefficient remains constant up to 25° C., we obtain for this temperature 0.7495 v. as the standard potential of the quino-quinhydrone electrode. Using these temperature coefficients and the standard potentials at 18° C. obtained by Bärlman and Lund and by Sørensen, Sørensen and Lindström-Lang, *viz.* 0.6179 v.³ and 0.6191 v.⁴ for the hydro-quinhydrone electrode and 0.7562 v.³ and 0.7548 v.¹ for the quino-quinhydrone electrode, the values obtained for 25° C. are 0.6134 and 0.6146 v. (hydro-quinhydrone) and 0.7562 and 0.7488 v. (quino-quinhydrone). For the hydro-quinhydrone electrode, these values are in fair agreement with the present result; the more serious discrepancy for the quino-quinhydrone electrode may be due to either an incorrect value of the temperature-coefficient or, more probably, uncertainty in the present value due to interaction of quinone and nitric acid.

Summary.

By E.M.F. measurements of cells involving the hydro-quinhydrone and quino-quinhydrone electrodes, the salt error of the quinhydrone electrode at 25° C. in aqueous HNO_3 solutions of concentration $c = 0.05 - 1.0$ N. has been determined; the salt error is proportional to the acid concentration, according to the equation $\Delta E_{\text{HNO}_3} = -0.0052_c$ volt. Previous determinations of the salt error in HCl have been confirmed by this method.

With the aid of the glass electrode, the quinhydrone electrode salt error in aqueous KNO_3 solutions has been found to be given by $\Delta E_{\text{KNO}_3} = -0.0038_c$ volt. Previous determinations of the salt error in potassium chloride solutions have been confirmed by this method.

The additivity of salt errors in mixed solutions of hydrochloric acid and potassium nitrate has been demonstrated.

The standard potentials of the hydro-quinhydrone and quino-quinhydrone electrodes at 25° C. have been determined as 0.6141 and 0.7459 volt respectively.

The author wishes to thank the Chemical Society for a research grant, Principal H. Richardson for his valuable help in facilitating this work, and M. A. Berry, Esq., B.Sc., for carrying out the preliminary hydrogen electrode measurements.

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THE THALLOUS-THALLIC REDOX POTENTIAL IN NITRIC AND PERCHLORIC ACIDS.

By H. I. STONEHILL.

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Since the determination by Partington and Stonehill¹ of the thallous-thalllic redox potential in aqueous H_2SO_4 ($c = 0.0125 - 1.0$ mol/l.) at 25° C., the redox potential in aqueous HClO_4 ($0.5 - 1.2205$ m) has been measured by Sherrill and Haas,² and in 0.5-2.0 m aqueous HNO_3 .

¹ Partington and Stonehill, *Trans. Faraday Soc.*, 1935, 31, 1357.

² Sherrill and Haas, *J.A.C.S.*, 1936, 58, 952.

by Noyes and Garner.³ Sherrill and Haas, who also made some determinations in H_2SO_4 which confirmed those of Partington and Stonehill, used the cell

Pt, H_2 (1 atm.) | $HClO_4$ (m) | $HClO_4$ (m), $Tl(ClO_4)_3$ (m_1), $Tl(ClO_4)_3$ (m_2) | Pt, and, calculating the hydrogen electrode potential on the assumption that $\gamma_{H^+} = \gamma_{HClO_4}$, (γ^- activity coefficient for the m or mol./1000 g. H_2O concentration scale), expressed their results for the potential of the redox electrode at $25^\circ C.$ in the form

$$E_{\text{redox}} = E_i^\circ + \frac{RT}{2F} \ln \frac{m_2}{m_1} \quad (1)$$

where $E_i^\circ = 1.2466 + 0.00761 + 0.00482I^\circ$ (2)

and $I = \frac{1}{2} \sum m_i x_i^2$, the molal ionic strength. Equation (2) held good approximately for $I = 0.5 - 1.4$. Liquid junction potentials were either ignored or else evaluated by an approximate experimental method. Noyes and Garner employed the cell

Pt, H_2 (1 atm.) | $HClO_4$ (m') | HNO_3 (m), $Tl(NO_3)_3$ (m_1), $Tl(NO_3)_3$ (m_2) | Pt; the hydrogen electrode potential was again calculated by assuming $\gamma_{H^+} = \gamma_{HClO_4}$ and the liquid junction potential E_L obtained by the equation

$$E_L = \frac{(2I_H - 1)RT}{F} \ln \frac{\gamma_{HNO_3} \cdot m}{\gamma_{HClO_4} \cdot m'} \quad (3)$$

which neglects any contribution due to the thallium salts. The results could be expressed by the equation

$$E_{\text{redox}} = E^\circ + \frac{RT}{2F} \ln \frac{m_2}{m_1} \quad (4)$$

where E° was practically constant over the range $m = 0.5 - 2.0$, $I = 1.09 - 2.17$, with the value 1.2303 ± 0.0007 v. at $25^\circ C.$ and 1.293 ± 0.001 v. at $0^\circ C.$

De Vault⁴ has pointed out that the values of γ_{HClO_4} due to Pearce and Nelson⁵ used in both these investigations are in error; the use of recalculated values alters the hydrogen electrode potentials and thus the redox potentials by $0.5 - 1.8$ mv. A further small correction ($0.1 - 0.3$ mv.) to the results of Noyes and Garner arises when the liquid junction potentials are calculated with the newer γ_{HClO_4} values along with the more accurate γ_{HNO_3} values of Hartmann and Rosenfeld⁶ instead of those of Abel, Redlich, and von Longyel.⁷

In view of the uncertainty in the results of these investigations due to liquid junction potentials, which were sometimes considerable in magnitude (e.g., 0.0147 v. in some of Noyes and Garner's cells), and in order to investigate the possibility of extending the measurements to lower acid concentrations, new determinations were made of the redox potential in $HClO_4$ and HNO_3 ($1.0 - 0.1$ mol./l.) at $25^\circ C.$ by a method which eliminates liquid junction potentials. The cells employed were

(A) Pt | $TlClO_4$ (c_1), $Tl(ClO_4)_3$ (c_2), $HClO_4$ (c) | $HClO_4$ (c) | Pt, H_2 (1 atm.) and

(B) Pt | $TlNO_3$ (c_1), $Tl(NO_3)_3$ (c_2), HNO_3 (c) | HNO_3 (c), quinhydrone (sat.) | Pt.

³ Noyes and Garner, *J.A.C.S.*, 1936, 58, 1268.

⁴ De Vault, *ibid.*, 1938, 60, 2551.

⁵ Pearce and Nelson, *ibid.*, 1933, 55, 3075.

⁶ Hartmann and Rosenfeld, *Z. physik. Chem.*, 1933, 164, 377.

⁷ Abel, Redlich and von Longyel, *ibid.*, 1928, 132, 189.

A recent determination⁸ enables allowance to be made for the salt error of the quinhydrone electrode in HNO_3 . The procedure used previously¹ to eliminate liquid junction potentials was employed, as follows: throughout the measurements with a given acid, the ratio c_2/c_1 was kept constant; for each acid concentration, a series of cells with gradually decreasing thallium content was measured, and the E.M.F.s were extrapolated to zero thallium content, when the liquid contact potential vanishes.

Experimental.

Approximately 2 N. stock solutions of Analar HNO_3 and HClO_4 were standardised volumetrically, using Na_2CO_3 solution and methyl orange, against a solution of Analar HCl which was standardised gravimetrically with AgNO_3 . Commercial TiNO_3 was recrystallised six times from conductivity water. About 0.7 g. mol. was dissolved in 500 c.c. N. HNO_3 , and ozonised oxygen was bubbled through it until about half was oxidised to thallic salt. Thallous perchlorate was prepared by fuming some purified TiNO_3 twice with 60% HClO_4 , then recrystallising from conductivity water. A suitable quantity was then ozonised in solution in N. HClO_4 , until about half converted to thallic salt. The two stock thallous-thallic-acid solutions thus obtained were analysed as follows: Thallous ion was estimated in an aliquot by titrating at 50-60°C. with standard KBrO_4 (made by dissolving a weighed amount of Analar salt in a definite volume) and methyl orange indicator, after adding some KCl and H_2SO_4 (method of Noyes, Pitzer and Dunn⁹). Total Tl was determined by first reducing thallic ion with SO_2 (10 min.), then boiling off excess (20 min.) and titrating with KBrO_4 . Since HNO_3 reacts with SO_2 , reduction of the nitrate solution was preceded by fuming with concentrated H_2SO_4 to remove nitrate. Free acid was determined⁸ by shaking a portion 3-4 min. with solid KCl and redistilled mercury to reduce thallic ion to thallous, filtering, washing the precipitate with water till acid free, and titrating filtrate plus washings with standard sodium carbonate. All cell solutions were made up by volume dilution from the stock acid and thallium solutions, using conductivity water.

The cell and auxiliary apparatus were as described elsewhere.⁸ The outer cell compartment contained the thallium solution and two bright wire electrodes, one platinum, the other gold. The inner compartment contained the pure acid solution; for HClO_4 the hydrogen electrodes, etc., were as previously described;⁸ for HNO_3 they were replaced by a bright gold and a bright platinum wire, and excess recrystallised quinhydrone⁸ was added to the acid; the gas inlet tube was removed and the bubbler outlet closed by a rubber stopper.

Cells were measured at 25 \pm 0.01°C. to 0.1 mv. for 12-36 hr. There was no significant difference in the potentials, obtained with gold and with platinum for both the quinhydrone and the redox electrodes. The E.M.F. reached equilibrium generally within 1-2 hr., remaining constant within 0.1 mv. for at least 6 hr., although in the nitrate cells there was a subsequent steady rise of about 0.1 mv. per hr., probably because of interaction of quinhydrone and nitric acid. Occasional duplicate cells which were set up agreed within 0.1 mv.

Results and Discussion.

The results for perchloric and nitric acids are given in Tables I and II respectively. E is the E.M.F. of the cell, corrected to 1 atm. partial pressure of hydrogen, in the case of the hydrogen electrode cells, by subtracting $\frac{RT}{2F} \ln \frac{p_{\text{H}_2}}{p_{\text{H}_2^{\circ}}}$, where p_{H_2} , the partial pressure of hydrogen in atm., was

⁸ Stonehill, *Trans. Faraday Soc.*,

⁹ Noyes, Pitzer, and Dunn, *J.A.C.S.*, 1935, 57, 1232.

TABLE I.—RESULTS FOR THALLIUM PERCHLORATES IN PERCHLORIC ACID.

 $(c_2/c_1 = 0.9331; (RT/2F) \ln(c_2/c_1) = 0.0009 \text{ v.})$

c_1	c_2	E (v.)	E_A' (v.)	γ_{HClO_4}	E_A'' (v.)	$\frac{0.1108\sqrt{2}}{x + x^{1/2}\sqrt{2}}$	E_A''' (v.)
1.0	0.02214	1.2631	1.2614	0.8182	1.2583	0.0519	1.3102
	0.002215	1.2624					
	0.0005538	1.2620					
0.5	0.01107	1.2750	1.2753	0.7577	1.2520	0.0440	1.2900
	0.001108	1.2755					
	0.0002769	1.2755					
0.2	0.004428	1.2938	1.2931	0.7661	1.2460	0.0338	1.2708
	0.0004430	1.2932					
	0.0001108	1.2925*					
0.1	0.002214	1.3044	1.3040	0.7960	1.2400	0.0268	1.2668
	0.0001108	1.3042					
	0.00002770	1.3034*					
0.05	0.0002214	1.3118	1.3108	0.8302	1.2300	0.0307	1.2507
	0.00008857	1.3108					
	0.00005536	1.3097*					
0.02	0.0002214	1.3175	1.3174	0.8752	1.2144	0.0143	1.2287
	0.0001107	1.3160*					
	0.00004428	1.3134*					
0.01	0.0001107	1.3155	1.3156	0.9046	1.1956	0.0106	1.2062
	0.00005536	1.3156					

TABLE II.—RESULTS FOR THALLIUM NITRATES IN NITRIC ACID.

 $(c_2/c_1 = 1.1186; (RT/2F) \ln(c_2/c_1) = 0.0014 \text{ v.})$

c_1	c_2	E (v.)	E_B' (v.)	γ_{HNO_3}	E_B'' (v.)	$\frac{0.1108\sqrt{2}}{x + x^{1/2}\sqrt{2}}$	E_B''' (v.)
1.0	0.02043	0.5400	0.5430	0.7246	1.2287	0.0484	1.2771
	0.002044	0.5440					
	0.0005110	0.5430					
	0.0002044	0.528*					
0.5	0.01021	0.5663	0.5653	0.7104	1.2347	0.0415	1.2702
	0.001022	0.5656					
	0.0002555	0.5654					
	0.0001022	0.553*					
0.2	0.004086	0.5892	0.5901	0.7532	1.2385	0.0323	1.2708
	0.0008174	0.5898					
	0.0002044	0.580*					
	0.0001034	0.5880*					
0.1	0.002043	0.6043	0.6044	0.7905	1.2363	0.0258	1.2621
	0.0004087	0.6044					
	0.0001022	0.6037*					
0.05	0.001021	0.6126	0.6124	0.8277	1.2282	0.0202	1.2484
	0.0005107	0.6126					
	0.0001021	0.6125					
	0.00002554	0.608*					
0.02	0.0001021	0.6172	0.6172	0.8750	1.2111	0.0140	1.2251
	0.00002554	0.6158*					
0.01	0.0001021	0.6203	0.6203	0.9053	1.1973	0.0104	1.2077
	0.00002554	0.6175*					

obtained by subtracting the vapour pressure of aqueous HClO_4 , as given by Pearce and Nelson,⁶ from the barometric pressure. E' is the voltage obtained by extrapolating at a given acid concentration to zero thallium content; the results marked with an asterisk, which were omitted in this extrapolation, are obviously poor, due either to thallic salt hydrolysis or to indefiniteness associated with the necessarily very low thallium concentrations.

Assuming that f_{H^+} , f_{Hg} for either acid (f activity coefficient corresponding to the c or mol/l. concentration scale), we have

$$E_A' = E_A^\circ + \frac{RT}{2F} \ln \frac{c_3}{c_1} + \frac{RT}{2F} \ln \frac{f_1}{f_1} - \frac{RF}{F} \ln cf_{\text{HNO}_3} (5)$$

for cell A, and

$$E_B' = E_B^\circ + \frac{RT}{2F} \ln \frac{c_3}{c_1} + \frac{RT}{2F} \ln \frac{f_1}{f_1} - \frac{RT}{F} \ln cf_{\text{HNO}_3} - 0.69938 + 0.0053 c (6)$$

for cell B; R , T and F have the usual significance, the subscripts 1 and 3 indicate thallic and thallic ions respectively, E_A° and E_B° are true standard redox potentials, and in equation (6) the last two terms are respectively the quinhydrone electrode standard potential¹⁰ and salt error in nitric acid.⁸ We may thus derive the quantities

$$E_A'' = E_A' + \frac{RT}{F} \ln cf_{\text{HNO}_3} - \frac{RT}{2F} \ln \frac{c_3}{c_1} = E_A^\circ + \frac{RT}{2F} \ln \frac{f_3}{f_1} (7)$$

and

$$\begin{aligned} E_B'' &= E_B' + \frac{RT}{F} \ln cf_{\text{HNO}_3} - \frac{RT}{2F} \ln \frac{c_3}{c_1} + 0.69938 - 0.0053 c \\ &= E_B^\circ + \frac{RT}{2F} \ln \frac{f_1}{f_1} \end{aligned} (8)$$

Values of cf for the two acids, required in order to evaluate E'' , were obtained as follows: The density-per cent. composition data from *International Critical Tables*¹¹ for aqueous HNO_3 and from Markham¹² for aqueous HClO_4 at 25° C. up to about $c = 1$ were fitted respectively to the equations

$$m/c = 1.002938 + 0.020855 c + 0.001142 c^2 (9)$$

and

$$m/c = 1.002938 - 0.044800 c - 0.001985 c^2 (10)$$

from which m could be calculated for a given c , and the corresponding value of γ read off a large-scale graph of γ vs. m . The value of cf could then be calculated by the equation

$$cf = m\gamma d_0 (11)$$

where $d_0 = 0.99707$ is the density of water at 25° C. Values of γ_{HNO_3} for given m were obtained from Hartmann and Rosenfeld.⁹ Up to $m = 0.5$ it was assumed¹³ that $\gamma_{\text{HClO}_4} = \gamma_{\text{HNO}_3}$, the latter being obtained from Robinson and Flarned;¹⁴ above 0.5 m , Rosenfeld's values¹⁴ for γ_{HClO_4} were used.

Values of E_A'' and E_B'' are given in Tables I and II; they are the potentials of the redox electrodes reduced to equal concentrations of thallic and thallic ions, and thus correspond respectively to the formal redox potentials E_1° of Sherrill and Haas and E° of Noyes and Garner, except for the correction involved in using cf instead of $m\gamma$ for the hydrogen

¹⁰ Horváth and Dearing, *J.A.C.S.*, 1935, 57, 447.

¹¹ *Int. Crit. Tables*, 1928, 3, 58.

¹² Markham, *J.A.C.S.*, 1941, 63, 874.

¹³ Robinson and Flarned, *Chem. Rev.*, 1941, 28, 419.

¹⁴ Landolt-Bornstein *physik. Tab.*, *Erg. B.* III, 1930, 2144.

ion activity; by equations (7), (8) and (11) this correction is $-\frac{RT}{F} \ln d_0 \approx 0.07$ mv., which is of the order of the experimental error and may thus be neglected.

In Fig. 1 the values of E_A'' are plotted against the ionic strength $I = \frac{1}{2}ac$. The values of E_A'' (corrected for newer γ_{HClO_4} values) for those cells of Sherrill and Haas with the minimum liquid junction potentials (i.e., the least thallium) and for those in which an adjustment has been attempted for the liquid junction potentials, are also plotted; they fall about 2 mv. above the curve of E_A'' vs. I , up to about $I \approx 1.05$; similarly, the corrected E'' values of Noyes and Garner when plotted against I (their values of which are in error) fall about 2 mv. below the curve of E_A'' vs. I up to about $I \approx 1.08$; this may be considered a fair agreement with the present results, in view of the liquid contact potential uncertainties in the earlier investigations.

From equations (7) and (8) it would appear that, since at low ionic strength the term $\frac{RT}{2F} \ln \frac{f_2}{f_1}$ is proportional to \sqrt{c} , an extrapolation of E'' against \sqrt{c} to zero c should give E^* , the true standard redox potential. Such an extrapolation would also eliminate the uncertainty due to the arbitrary assumption that $f_{\text{H}^+} = f_{\text{Hx}}$ since at zero ionic strength $f_{\text{H}^+} = f_{\text{Hx}}$. However, it is clear that below about $c = 0.2$ there is a considerable uncertainty in the E'' values for both acids, due to thallium salt hydrolysis and the experimental difficulties arising from the necessity of keeping thallium concentrations low in order to minimise hydrolysis and liquid contact potentials. At lower ionic strengths the term $\frac{RT}{2F} \ln \frac{f_2}{f_1}$, which is negative, should decrease numerically as c decreases, and thus E'' should increase with fall in c , contrary to what is observed. This extrapolation, then, is not possible.

Another method of extrapolation is suggested by the following considerations. Values of γ_{HClO_4} and γ_{HNO_3} up to $m = 1$ have been fitted, with a maximum error of 0.2% in γ , to the Hückel type of equations¹⁵

$$-\log \gamma_{\text{HClO}_4} = \frac{0.5065 \sqrt{c}}{1 + 1.31 \sqrt{c}} - 0.1480c + \log(1 + 0.036m) . \quad (12)$$

$$\text{and } -\log \gamma_{\text{HNO}_3} = \frac{0.5065 \sqrt{c}}{1 + 1.475 \sqrt{c}} - 0.0802c + \log(1 + 0.036m) . \quad (13)$$

¹⁵ Hückel, *Physik. Z.*, 1925, 26, 93.

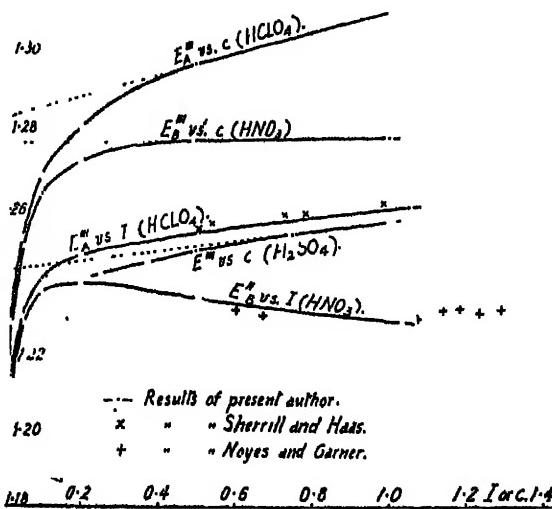


FIG. 1.

If it is assumed that a similar type of equation may be applied to single ion activity coefficients, then for Tl^+ and Tl^{3+} present to an infinitesimal extent in HClO_4 or HNO_3 , of concentration c we have

$$\log \gamma_1 = \frac{0.5065 \sqrt{c}}{1 + A\sqrt{c}} - B_1 c + \log(1 + 0.030m) \quad . . . \quad (14)$$

$$-\log \gamma_3 = \frac{0.5065 \sqrt{c}}{1 + A\sqrt{c}} - B_3 c + \log(1 + 0.030m) \quad . . . \quad (15)$$

where B_1 and B_3 are constants and A has the value appropriate to the acid concerned, i.e. 1.31 or 1.475. Thus

$$-\frac{RT}{2F} \ln \frac{f_3}{f_1} = -0.02958 \log \frac{\gamma_1}{\gamma_3} = \frac{0.1198 \sqrt{c}}{1 + A\sqrt{c}} - (B_3 - B_1)c \quad . . . \quad (16)$$

and by equations (7) and (8),

$$E''' - E'' + \frac{0.1198 \sqrt{c}}{1 + A\sqrt{c}} - E^\circ + (B_3 - B_1)c \quad . . . \quad (17)$$

so that E''' should give a linear plot against c , and extrapolate at $c = 0$ to E° . Values of $(0.1198 \sqrt{c})/(1 + A\sqrt{c})$ and of E''' are given in the last two columns of Tables I and II, and E''' is plotted against c for both acids in Fig. 1. There is a progressive deflection from the straight line as c falls below about 0.3. If we assume that the points for the two higher concentrations can be relied upon to fix the straight line, we obtain for $c = 0$ the values $E_A^\circ = 1.2818$ v. and $E_B^\circ = 1.2753$ v., which are surprisingly close in view of the uncertainties involved, and suggest that the true standard redox potential, E° , has the same value, about 1.280 v., in both perchloric and nitric acids.

An attempt was made to treat the data for sulphuric acid solutions² in the same way; the value 3.64×10^{-8} cm. was used for the mean ionic diameter in order to fix the constant A of equation (17), and it was assumed as a very crude approximation that sulphuric acid could be treated as a binary electrolyte. The straight line fixed by the points for the highest two concentrations leads at $c = 0$ to the value $E^\circ = 1.242$ v. which, although far less reliable than the corresponding values for perchloric and nitric acids, is significantly lower, probably because of a greater degree of complex ion formation. Allowance for the secondary dissociation of sulphuric acid by the method of Scatchard and Epstein,¹⁸ using their value of 1.5 for A , leads by a similar treatment to almost the same result, $E^\circ = 1.239$ v.

Summary.

The formal thallous-thallic redox potential has been determined at 25° C. in both perchloric and nitric acids at concentrations 1.0–0.1 mol/l. by methods which eliminate liquid junction potentials. Thallic salt hydrolysis and the necessary use of low thallium concentrations to minimise liquid junction potentials render the measurements increasingly unreliable as the acid concentration falls below 0.2 mol/l. The results are in fair agreement with those of Sherrill and Hnas for perchloric acid and of Noyes and Garner for nitric acid, considering the uncertainties due to liquid junction potentials in those. Assuming the applicability of the Hückel modification of the Debye-Hückel equation for single ion activity coefficients, it is estimated that the true standard redox potential has roughly the same value, i.e. 1.280 v., in both perchloric and nitric acids,

¹⁸ Scatchard and Epstein, *Chem. Rev.*, 1942, 30, 221.

but the value is apparently considerably lower in sulphuric acid, probably because of enhanced complex ion formation.

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BOND ENERGY, BOND DISTANCE, AND THE NATURE OF THE COVALENT LINKAGE.

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The available theoretical methods do not allow a quantitative treatment of the actual states of molecules more complicated than hydrogen. They have been, therefore, described in terms of classical structures which would allow the calculation at least of the change in stability of the actual state, this change being assumed to be due to their interaction.

For certain structures, e.g. those of aromatic and conjugated systems, a successful mathematical treatment of these so-called resonance energies has been carried out using certain assumptions and approximations, the value of which is uncertain, until the assumed qualitative structures on which it is based are empirically confirmed. Such a treatment does not prove the structures, but can only show that the qualitative conclusions arrived at are justified by the present theoretical conceptions.

Originally a working hypothesis, this idea has meantime been generalised¹ and claimed to be a fundamental extension of the empirical structural theories. This theory of resonance or resonance hybrids can be described as follows. The actual structure of chemical molecules is a hybrid (or intermediate state) between the possible idealised^{*} structures. Two different types of "resonance" are distinguished: (i) *Resonance involving one special linkage*, the contributing states being distinguished by a difference in bond type. Thus, one state may be of the covalent type, the other of the ionic type, e.g. the hydrogen molecule, hydrogen fluoride, or acetone may be represented by hybrids as indicated in I, II and III.

(I) $\text{H}-\text{H} \leftrightarrow \text{H}^+ \text{H}^-$; (II) $\text{H}-\text{F} \leftrightarrow \text{H}^+\text{F}^-$; (III) $\text{Me}_2\text{C} \cdot \text{O} \text{--} \text{Me}_2\text{C} \cdot \text{O}^-$.

(ii) Resonance involving an interrelated change of numerous linkages of a molecule, the so-called *resonance of molecules among several bond structures*, e.g. the benzene molecule may represent a hybrid between the two possible Kekulé structures, and the three possible Dewar structures.

Of the numerous possible structures, that of greater stability should best represent the actual structure, but the less stable structures should contribute to a degree corresponding to their stability. If two or more

* The structures developed by the empirical atomic and electronic structural theories, e.g. the so-called Lewis-Langmuir structures, possess only a qualitative significance. They do not purport to indicate that the bond properties (e.g. bond energy) of a certain linkage are quantitatively identical in all substances. The structure used in the description of resonance hybrids are, therefore, idealised structures.

¹ Pauling, *The Nature of the Chemical Bond*, New York, 1940.

structures of similar stability are possible, they would contribute to a similar degree, but the energy would be less by a certain amount called the *resonance energy* of the system, due to the interaction (resonance) between the various contributing structures. In addition, the bond length of a linkage within the actual structure should be intermediate between that of the contributing structures but, partly owing to the stabilising effect of the resonance, should be nearer to the smaller of the possible distances.

It is not accidental that these two types of resonance are mainly connected with the two types of systems, namely covalent bonds different from the ideal ionic and ideal covalent linkage, and conjugated systems and related structures, which cannot be satisfactorily expressed by an ideal classical structure. They attempt to solve the empirical problems, which must precede any possible quantitative or semi-quantitative treatment, by describing in the former case the type of forces responsible for the stability of covalent linkages, in the latter case the actual qualitative structure in terms of ideal classical structures.

The hypothesis of the existence of resonance hybrids is not a necessary theoretical development of wave-mechanics. It is a speculative extension of the interpretation of the nature of the covalent linkage or the covalent forces by Heitler and London,³ the interchange of the two electrons involved in the linkage giving cause for the so-called exchange energy. It is not supported by any full quantitative treatment. It remains to be seen whether it is supported by facts.

An attempt has been made to derive evidence for the interpretation of the structure of molecules as resonance hybrids involving an increased stability due to the resonance energy from the bond properties of the molecules, especially the *bond energies* and *bond distances*. Undoubtedly, the bond energies should serve as a test for the existence of the so-called resonance energy, and the bond distances as a test for the suggested contributing idealised resonance structures. The bearing of these properties on the elucidation of the nature of the covalent linkages will now be discussed.

1. Bond Energies.

The bond energies used are those given by Pauling⁴ (*cf.* Tables I and II). They are assumed to be approximately constant within different molecules if the type of linkage is not changed. In discussing the relationship between bond energies of different linkages the postulate of the *additivity of normal covalent bonds*⁴ is accepted. It is assumed that the arithmetic mean of the two bond energy values $D(A-A)$ and $D(B-B)$ is the energy of an ideal normal covalent bond between the unlike atoms A and B. The observed bond energies of the linkages between two unlike atoms A and B deviate considerably from such ideal hypothetical values, generally showing an increase (Table I).

According to Pauling⁵ the elements can be arranged in such order that this increase (Δ) of the observed bond energy as compared with the ideal hypothetical value becomes greater the further away the atoms A and B are in the scale. The suggested scale corresponds qualitatively to the property, which indicates the power of an atom to attract electrons to itself, and is, therefore, called the *electronegativity scale* (*cf.* Table II).

This is an empirical scale based on the observed values of the bond energies of different linkages and their deviations from the additivity postulate of covalent linkages and is chosen to give the best possible agreement with the observed values. However, it shows a simple qualitative relationship to the position of the elements in the periodic

³ Heitler and London, *Z. Physik*, 1927, 44, 455.

⁴ *Loc. cit.*¹, p. 53; *J. Am. Chem. Soc.*, 1932, 54, 3570.

⁴ *Loc. cit.*¹, p. 48.

⁵ *Loc. cit.*¹, p. 58.

system. The electronegativity increases within the periods of the system with increasing atomic number, e.g. from Li to F, and within the groups

TABLE I.

Linkage.	Obs. Bond Energy.	$\frac{D(A-A) + D(B-B)}{2}$	A.	$\sigma = \log \frac{J_A}{J_B}$	$J_A - J_B$	$\sqrt{D(A-A, B-B)}$	B.
Li-II	57.7	65.3	-	7.6	1.1	53.0	1.7
Na-II	52.3	60.9	-	8.6	1.2	43.6	8.7
K-II	44.5	58.0	-	13.5	1.3	36.1	5.4
C-II	87.3	81.0	-	6.3	0.52	0.4	9.5
Si-II	75.1	73.0	-	2.1	0.30	0.3	0.2
N-H	83.7	61.7	22.0	0.98	0.0	45.6	38.1
P-II	63.0	61.2	-	1.8	0.28	0.0	18.8
As-II	47.3	50.3	-	12.0	-	30.0	7.7
O-II	110.2	60.2	41.0	1.13	1.4	60.2	50.0
S-H	87.5	83.6	-	3.0	0.41	0.4	6.1
Se-II	73.0	80.5	-	7.5	-	77.2	-4.2
F-II	147.5	83.5	64.0	1.07	1.0	81.0	66.5
Cl-II	102.7	80.6	32.1	0.98	0.0	77.3	25.4
Br-II	87.3	74.8	12.5	0.74	0.7	64.0	18.3
I-II	71.1	69.8	1.6	0.20	0.4	63.2	10.2
Si-C	57.6	50.6	7.0	0.55	0.7	50.0	7.6
N-C	48.6	39.3	9.3	0.04	0.5	34.2	14.4
O-C	70.0	46.8	23.2	1.00	1.0	45.2	24.8
S-C	54.5	61.2	-	6.7	-	61.1	-1.6
F-C	107.0	61.1	45.0	1.41	1.5	61.0	40.0
Cl-C	66.5	58.2	8.3	0.61	0.5	58.2	8.3
Br-C	54.0	52.4	1.6	0.26	0.3	52.0	2.0
I-C	45.5	47.4	-	1.0	-	40.1	-0.6
O-Si	89.3	38.7	50.6	1.48	1.7	38.5	50.8
S-Si	60.0	53.2	7.7	0.58	0.7	52.1	8.8
F-Si	143.0	53.0	90.0	1.97	2.2	52.0	91.0
Cl-Si	85.8	50.2	35.6	1.21	1.2	49.0	36.2
Br-Si	69.3	44.3	25.0	1.04	1.0	44.3	25.0
I-Si	51.7	39.4	11.7	0.71	0.7	39.2	11.9
Cl-Ge	104.7	50.2	53.0	1.53	1.2	49.6	54.5
M-N	68.8	41.8	27.0	1.08	1.0	35.7	33.1
Cl-N	38.4	38.9	-	0.5	-	34.0	4.4
Cl-P	62.8	38.4	24.4	1.03	0.9	33.1	29.7
Br-P	40.2	32.5	16.7	0.85	0.7	40.5	10.7
I-P	35.2	27.6	7.6	0.58	0.4	26.2	9.0
Cl-As	60.3	36.5	23.8	1.01	1.0	33.3	27.1
Br-As	48.0	30.6	17.4	0.87	0.8	26.4	21.0
I-As	33.1	25.7	7.4	0.57	0.5	23.4	9.7
F-O	58.6	49.2	9.4	0.64	0.5	47.1	11.5
Cl-O	49.3	40.4	2.9	0.36	0.5	44.9	4.4
Cl-S	66.1	60.8	5.3	0.48	0.5	60.7	5.4
Br-S	57.2	55.0	2.2	0.31	0.3	54.3	2.0
Cl-Se	66.8	57.7	9.1	0.03	0.6	57.7	9.1
Cl-F	86.4	60.7	25.7	1.05	1.0	60.6	25.8
Cl-Br	52.7	52.0	0.7	0.18	0.2	51.6	1.1
Cl-I	51.0	47.0	4.0	0.42	0.5	45.7	5.3
Br-I	42.9	41.2	1.7	0.27	0.3	40.9	2.0

with decreasing atomic number, e.g. from I to F. Only the relationship between the atoms of different groups and periods remains less certain.

Pauling has attributed to the different elements certain quantitative

TABLE II

- 2.1 1st row : Electronegativity.⁶
 10.3 2nd row : Observed bond energy of A - A in K.cal./mol.³
 0.37 3rd row : One half of observed interatomic distance of A - A in Angstrom.²³
 0.30 4th row : Covalent radius (Pauling-Huggins).¹⁰
 0.37 5th row : Covalent radius (Schomaker Stevenson).¹²
 0.0 6th row : Cation crystal radius (Pauling).¹¹
 2.08 7th row : Anion crystal radius (Pauling).¹³

Li	B	C	N	O	F
1.0	2.0	2.5	3.0	3.5	4.0
1.72	-	58.0	20.0	34.0	63.5
1.34	0.80 (1) ²¹	0.77	0.74	0.74	0.72
-	0.88	0.77	0.70	0.66	0.64
1.34	0.82 *	-	0.74	0.74	0.72
0.60	0.20	0.15	0.11	0.09	0.07
-	-	2.00	1.71	1.40	1.30
Na	Si	P	S	Cl	
0.9	1.8	2.1	2.5	3.0	
1.84	42.5	18.0	63.8	57.8	
1.54	1.17	1.10	1.05	0.99	
-	1.17	1.10	1.04	0.99	
1.54	-	-	-	-	
0.95	0.41	0.34	0.29	0.26	
-	2.71	2.12	1.84	1.81	
K	Ge	As	Se	Br	
0.8	1.8	2.0	2.4	2.8	
1.26	42.5	15.1	57.6	46.1	
1.96	1.22	1.22	1.10	1.14	
-	1.22	1.21	1.17	1.14	
1.96	-	-	-	-	
1.33	0.53	0.47	0.43	0.39	
-	2.72	2.22	1.98	1.95	
Rb	Su	Sb	Te	I	
0.8	1.7	1.8	2.1	2.5	
-	-	-	-	3.0	
-	1.40	1.43	1.38	1.33	
-	1.40	1.41	1.37	1.33	
2.11	-	-	-	-	
1.48	0.71	0.62	0.50	0.50	
-	2.04	1.45	2.21	2.16	

values of the electronegativities (Table II). These have been chosen to satisfy best a relationship between the electronegativity difference of the atoms of a linkage ($X_A - X_B$) and the square roots of the energy increase expressed in electron volts as compared with the ideal covalent bond energy, i.e. $X_A - X_B$ should equal $0.208 \sqrt{\Delta}$, where Δ is the energy increase, expressed in k.cal./mol., and $0.208 \sqrt{\Delta}$ represents the square root of Δ expressed in electron volts. An additive constant has been so chosen as to give the first row elements C to F the values 2.5-4.0. Detailed discussion of this quantitative relationship can be omitted. There is, of course, no theoretical reason for the existence of such a quantitative relationship between $(X_A - X_B)$ and $\sqrt{\Delta}$, and such a quantitative relationship does not appear to be justified by the facts (*cf.* values in Table I).

There are numerous exceptions to the existence of such a simple *qualitative* relationship between (Δ) and $(X_A - X_B)$ of the atoms of a linkage.

* Suggested value : 0.85 Å according to Bauer and Beach.²⁰

(i) In many cases, e.g. Li—H, Na—H, K—H, As—H, Se—H, C—S, a decrease of the bond energy as compared with that of the ideal covalent linkage is observed. (ii) Linkages containing a hydrogen atom do not generally obey the suggested relationship. Irrespective of the electronegativity differences, the deviation (Δ) from the ideal covalent bond energy decreases within the groups with increasing atomic number of the second element, and within the periods with decreasing atomic number, often assuming negative values; in contrast to Pauling's rule the electronegativity difference increases from C—H to Li—H, from Li—H to K—H, from As—H to K—H, from P—H to Na—H, and from P—H to As—H (cf. Table III). The values for Ge—H, Sb—H and Te—H are not known,

TABLE III.

	Δ	$X_A - X_B$		Δ	$X_A - X_B$		Δ	$X_A - X_B$
Li—H	7.6	1.1	N—H	22.0	0.9	Se—H	7.5	0.3
Na—H	8.6	1.2	P—H	1.8	0.0	Te—H	?	0.0
K—H	-13.5	1.3	As—H	12.0	0.1	I—H	64.0	1.9
C—H	6.3	0.4	Sb—H	?	0.3	Cl—H	22.1	0.9
Si—H	2.1	0.3	O—H	41.0	1.4	Br—H	12.5	0.7
Ge—H	?	0.3	S—H	3.9	0.1	I—H	1.6	0.4

but should be of interest. Pauling's rule is possibly only valid for linkages which contain at least one atom of comparatively high electronegativity. Two atoms with small electronegativities may behave anomalously owing to their strong resistance to becoming negatively charged within the linkage. A knowledge of the bond energy of linkages including a carbon atom and one of lower electronegativity should be of interest in this connection.

Although a quantitative analysis and theoretical treatment does not appear to be possible at present, these results allow the deduction that the bond energy between unequal atoms is composed (i) of *covalent forces* interpreted in the case of the hydrogen molecule as exchange energy and (ii) of *ionic, i.e. Coulomb forces*. The former should decrease with increasing electronegativity difference, the latter increase. The frequently observed increased stability of a linkage with increasing electronegativity difference of its atoms may indicate that the increase due to the polar forces will be higher than the decrease of the covalent exchange energy. Actually, the position should be more complicated. In addition to the covalent and ionic forces, the bond energy should also consist of other forces, which in the case of the H₂ molecule amount to not less than 15 % of the total bond energy (called by Pauling their deformation energy). An increase of the bond energy due to the influence of the polar forces would easily be accompanied by a decrease due to deformation (or steric) effects, or the latter (possibly repulsive) effects may stabilise the molecule in a state where covalent or ionic forces contribute to a smaller extent.

The ionic character of linkages between unlike atoms has been interpreted⁴ by their existence as *resonance hybrids between ideal covalent and ionic structures*. The interaction between these structures should be responsible for an increased energy, the so-called ionic resonance energy.* The observed energy D (A—B) of a bond between the unlike atoms A and

* *Loc. cit.*,¹ p. 47.

* Pauling⁵ has already interpreted the small ionic terms contributing to the stability of a linkage between like atoms, e.g. of the hydrogen molecule, by resonance involving small amounts of the extreme ionic structures such as A⁺A⁻ and A⁻A⁺. The resultant small resonance energies are included in the energies of ideal covalent linkages.

¹ *Loc. cit.*,¹ p. 22.

B should, therefore, be always greater than (or equal to) the energy of the ideal covalent bond between these atoms, i.e. the difference

$$\Delta = D(A-B) - \frac{D(A-A) + D(B-B)}{2}$$

should never be negative.

This interpretation, though unsupported by an exact mathematical treatment, can be tested empirically. The following facts are, however, at variance with the above interpretation:

(1) The bond energy of linkages between unlike atoms is in many cases smaller than that expected for an ideal covalent linkage (*cf.* above).

An attempt has been made to overcome this difficulty by the introduction of an alternative hypothesis, namely, the adoption of the geometric rather than the arithmetic mean of the ideal covalent linkages, *i.e.* the energy of the ideal covalent linkage A-B should equal $\sqrt{D(A-A)D(B-B)}$. This, however, does not account for the observed "anomalies"; it only artificially decreases all ideal bond energies of covalent linkages to a degree dependent on the difference of the ideal covalent bond energy values $D(A-A)$ and $D(B-B)$ of the atoms A and B of a linkage. The modified deviations of the observed energies Δ' are also given in Table I. (i) It is true that the deviations (Δ') of the bond energies of Li-H, Na-H, K-H become positive, but the increase is now bigger for Na-H than for K-H with the bigger electronegativity difference. Furthermore, the observed increase of 4.7, 8.7, and 8.4 k.cal./mol. is much less than would be expected for electronegativity differences of 1.1, 1.2, and 1.3 respectively. Thus, all linkages with the smaller electronegativity difference 0.9 and 1.0 already show an increase of bond energy (Δ') varying between 24.0 and 38.0 k.cal./mol. and SiCl and GeCl with a difference of 1.2 an increase of 36.2 and 54.5 k.cal./mol. (ii). The values for Sc-H and C-S* remain negative. (iii) P-H with an electronegativity difference 0.0 now shows an increase by 18.8 k.cal./mol., which is also shown by H-Br and P-Br with an electronegativity difference 0.7, other linkages with 0.7 such as C-Si, Si-S, Si-I showing even the much smaller values 7.6, 8.8, and 11.9 k.cal./mol.

(2) Bond energy deviations of linkages involving a H atom do not generally concur with their electronegativity differences (*cf.* above and Table II). Again the use of the geometric mean does not overcome these "anomalies." On the contrary, additional anomalies would be noted, since P-H ($X_A - X_B$, 0.0) lying between Si-H ($X_A - X_B$, 0.3) and S-H ($X_A - X_B$, 0.4) would possess a higher energy increase (18.8 k.cal./mol.) than the latter (8.4) and 6.3 k.cal./mol.), and As-H ($X_A - X_B$, 0.1) would show the higher energy increase 7.7 k.cal./mol. than Se-H ($X_A - X_B$, 0.3) with -4.2 k.cal./mol.

(3) It may be argued that the observed "anomalies" cannot definitely exclude the interpretation of linkages as resonance hybrids involving ideal covalent and ideal ionic structures, since they may be due to the neglect of additional terms arising, for example, from the deformation of the electrons or nuclei. The observed bond energies, certainly, are not evidence for the existence of such resonance hybrids and resonance energies. Little justification exists for the introduction of a new fundamental hypothesis, which is unsupported by evidence and requires a number of auxiliary hypotheses, in order to account for the observed facts. Its incompatibility with the facts related to conjugated systems and light absorption of organic compounds is shown elsewhere.*

* Pauling¹ has given to the C-S linkage the values +6.7(Δ), 0.54 (0.208 $\sqrt{\Delta}$), -0.5 ($X_A - X_B$), which are due to an error, and should be replaced by -6.7, -0.0 respectively.

¹ *Loc. cit.* ¹, p. 59, Table II.—r.

* Burawoy, *Chem. Ind.*, 1940, 59, 594, 855.

(4) The resonance energy should reach its maximum when ideal covalent and ionic structures contribute equally. Having reached this point the ionic should become increasingly more stable than the covalent structure, whereas the actual resonance energy should decrease. The necessity to attribute the increased stability of linkages with their increasing polar character to different causes, according to whether 50% ionic character is reached or not, presents difficulty.

2. Bond Distances.

The discussion of bond distances will also be based on the *postulate of additivity*. The atoms within an ideal covalent linkage may possess constant atomic covalent radii, and the length of an ideal covalent linkage may be represented as the sum of the covalent radii of the atoms involved.

Pauling and Huggins¹⁰ have advanced a system of such covalent radii (Table II), which, excepting the first row elements other than carbon, are in satisfactory agreement with half the interatomic distances of elementary molecules or crystals.

In contrast to the bond energies of linkages between unlike atoms, which deviate from those expected for ideal covalent linkages, the observed distances of linkages should, according to Pauling,¹¹ generally obey the additivity rule expected for ideal covalent linkages. *Their ionic character should be of no influence.* Only in certain cases, e.g. the halides involving atoms of the second and lower rows of the periodic table and of boron, should the interatomic distances differ from (being in fact smaller), those expected for ideal covalent linkages, and require explanation (cf. Table IV).

However, as already realised by Schomaker and Stevenson,¹² the originally suggested atomic covalent radii of the first row elements other than C have to be considerably modified. Pauling has attributed to the H atom a covalent radius of 0.3 Å., an average value obtained from the bond lengths of a number of linkages involving the hydrogen atom. The observed bond length of the H₂ molecule, however, is 0.74 Å.; the empirical covalent radius of the H atom to be adopted is, therefore, 0.37 Å. Similarly, the covalent radius of the F atom to be adopted is 0.72 Å. as derived from the observed bond length of the molecule 1.45 Å., and not the lower value 0.68 Å. originally suggested. It is not justifiable to adopt the lower values and to consider the observed higher interatomic distances of the H and F molecules as anomalous. The original covalent values of N and O have also to be modified in view of recent interatomic distance measurements of H₂O₂ and hydrazine. The more correct values of covalent radii as modified and extended for the alkali metals by Schomaker and Stevenson are also given in Table II.

From these modifications it results that the observed interatomic distances for linkages between unlike atoms are generally shorter than those expected for ideal covalent linkages according to the additivity rule. The additivity rule for the actual bond distances was not based on evidence, but the covalent atomic radii of the first row elements other than C were arbitrarily chosen to agree with the additivity rule. Table IV shows the observed interatomic distances r_{A-B} , the ideal interatomic distances calculated with the old and new covalent radii ($r_A + r_B$ and $r'_A + r'_B$ respectively), and the deviations (Δ and Δ' respectively). Stevenson and Schomaker have rightly suggested that both the observed increase of the bond energies and the shortening of the interatomic distances as compared with the values expected for ideal covalent linkages have the same cause. Consequently, the electronegativity difference of the atoms of a linkage, i.e. the ionic character of the linkage, essentially also governs the shortening of the observed interatomic distances.

¹⁰ Z. Krist., A, 1934, 87, 205; loc. cit.¹, p. 164.

¹¹ Loc. cit.¹, p. 232.

¹² J. Am. Chem. Soc., 1941, 63, 37.

TABLE IV²⁰

Linkage		β_{AB}	$\beta_{AB} - \beta_{AC}$	$\beta_{AB} - \beta_{BC}$	$\beta_{AB} - \beta_{AC} - \beta_{BC}$
La—H .	1.00				
Na—H .	1.80				
K—H .	2.24				
Rb—H .	2.17				
C—H .	1.00				
Si—H .	1.42 (0)	1.07	0.02	1.71	0.11
N—H .	1.01	1.47	0.05(1)	1.51	0.02 (0.8)
P—H .	1.46 (0)	1.40	0.01	1.11	0.10
As—H .	1.56 (4)	1.51	-0.05 (3)	1.47	0.07 (7)
O—H .	0.97	0.96	0.01	1.11	0.14
S—H .	1.35	1.34	-0.01	1.41	0.06
Se—H .	1.50	1.47	-0.03	1.54	0.04
Br—H .	0.92	0.94	-0.02	1.00	0.17
Cl—H .	1.28	1.20	-0.01	1.30	0.08
Bi—H .	1.41	1.44	-0.03	1.51	0.10
I—H .	1.00	1.03	-0.03	1.70	0.10
B—C .	1.56	1.65	0.09	1.50	0.03
Si—C .	1.93	1.94	-0.01		0.06
Ge—C .	1.98	1.99	-0.01		0.07
Sn—C .	2.18	2.17	-0.01		0.07
N—C .	1.47	1.47	0.00	1.51	0.04
P—C .	1.87	1.87	0.00		0.04
As—C .	1.98	1.98	0.00		0.05
O—C .	1.42	1.43	-0.01	1.51	0.09 (2.80)
S—C .	1.82	1.81	+0.01		0.00
F—C .	1.39 (5)	1.41	-0.02 (5)	1.49	0.10 (3)
Cl—C .	1.76	1.76	0.00		0.05
Br—C .	1.91 (4)	1.91	+0.00 (3)		0.03
I—C .	2.12 (5)	2.10	+0.02 (5)		0.01
R—ST .	1.54	1.81	-0.27	1.80	0.25
Cl—Si .	2.00	2.16	-0.16		0.11
Br—Si .	2.14 (6)	2.31	-0.17 (2)		0.00
I—Si .	2.43	2.50	-0.07		0.06
Cl—Ge .	2.08	2.21	-0.13		0.12
Br—Ge .	2.32	2.36	0.04		0.10
I—Ge .	2.48	2.55	0.07		0.06
Cl—Sn .	2.30	2.30	0.00		0.14
Br—Sn .	2.41	2.51	0.10		0.15
I—Sn .	2.01	2.73	0.00		0.07
R—P .	1.53	1.74	0.22	1.82	0.30
Cl—P .	2.00	2.04	0.00		0.08
Br—I .	2.23	2.24	0.01		0.06
I—P .	2.47	2.43	-0.04		0.03
F—As .	1.72	1.85	0.13	1.46	0.05
Cl—As .	2.16	2.20	0.04		0.09
Br—As .	2.34	2.35	0.01		0.07
I—As .	2.34	2.54	0.00		0.04
Cl—Sb .	2.37	2.40	-0.03		0.11
Br—Sb .	2.50	2.55	-0.03		0.00
I—Sb .	2.71	2.74	-0.03		0.00
F—O .	1.41	1.30	-0.11	1.46	0.05
Cl—O .	1.68	1.65	+0.03	1.73	0.05
Cl—S .	1.90	2.03	-0.04		0.05
Cl—Te .	2.30	2.36	0.00		0.08
I—Cl .	1.64	1.63	+0.01	1.71	0.07
I—Cl .	2.32	2.32	0.00		0.05
F—B .	1.30	1.48	-0.18	1.54	0.24
Cl—B .	1.74	1.87	-0.13	1.81	0.07
Br—B .	1.87	2.02	-0.15	1.90	0.09

Actually, these authors advance the equation $r_{A-B} = r_A + r_B - \beta(X_A - X_B)$ where the constant β is assumed to be 0.09 and X_A and X_B are the electronegativities of the atoms of the linkage. The values for the expression $\beta(X_A - X_B)$ calculated with the electronegativity values derived by Pauling from the bond energy deviations are also given in Table IV. This expression has no theoretical basis and the chosen constant 0.09 is empirically found to be the most satisfactory in relation to all observations. As in the case of the bond energies, there is no quantitative agreement between the deviation (Δ') and the electronegativity difference of the linkages. In a few cases no deviation or even a slightly positive one is observed. The deviations for linkages involving a H atom are generally much higher, those involving a C atom much lower, those involving a halogen atom in some cases higher, and in others much lower, than calculated with the expression 0.09 ($X_A - X_B$).

In addition, many qualitative exceptions will be noted. Thus, the observed deviations and the electronegativity differences of linkages involving a H atom or halogen atom with atoms of the same group do not generally concur (for examples, compare Table V). The agreement

TABLE V

Linkage.	Δ' .	$X_A - X_B$.	Linkage.	Δ' .	$X_A - X_B$.
Cl—Si	0.16	1.2	Ge—Br	0.04	1.0
Cl—Ge	0.13	1.2	Ge—I	0.07	0.7
Cl—Sn	0.00	1.3	H—F	0.17	1.9
Br—Si	0.17 (2)	1.0	H—Cl	0.08	0.9
Br—Ge	0.04	1.0	H—Bi	0.10	0.7
F—P	0.22	1.0	H—I	0.10	0.4
F—As	0.13	2.0	B—F	0.21	2.0
Cl—P	0.09	0.9	B—Cl	0.07	1.0
Cl—As	0.04	0.10	B—Br	0.09	0.8
Cl—Sb	0.03	1.2	H—C	0.05	0.4
Cl—O	0.05	0.5	H—Si	0.12 (0.8)	0.3
Cl—S	0.04	0.5			
Cl—Te	0.00	0.9			

appears, however, to be sufficient to show that the *polar character of the linkages* as characterised by the electronegativity differences of their atoms is at least one, possibly the most important factor responsible for their shortening. Other factors already recognised in the case of the simple H molecule (e.g. the deformation of the nuclei and of the electrons, possibly related to the size and the type of charge of the atoms) may be responsible for the observed qualitative "exceptions" and the unsatisfactory quantitative agreement between bond energy increase, bond distance shortening and the electronegativity differences of the atoms of a linkage.

The ionic character of the linkages responsible for the deviations of the bond energies has been interpreted¹ as resonance between ideal covalent and ideal ionic structures. The conclusion that this type of resonance is generally without effect on the bond lengths has to be modified in the light of the new atomic radii. Ionic-covalent resonance, if existing, is accompanied by a shortening of the ideal covalent bond lengths.

Pauling has not discussed the changes of the bond distances to be deduced from the existence of this type of resonance. He has, however,

shown in other cases of resonance¹² that the interatomic distance of a linkage involving resonance between two structures should lie between the distances expected for these structures, but nearer to the lesser one, partly owing to the stabilisation due to resonance. Indeed, in discussing numerous other types of resonance, an empirical equation

$$R = R' + (R'' - R') \frac{1}{2X+1}$$

has been proposed, where R is the value of the interatomic distance for a bond of intermediate type (actual bond), R' and R'' those for the contributing resonating structures, and X the amount of the structure corresponding to R'' .

In Table IV the bond distances for the ideal ionic linkages based on the ionic crystal radii¹⁴ (Table II) are given. It will be noted that the ideal ionic bond distances are generally much *longer*, the observed bond distances *shorter* than the ideal covalent bond distances. Two important conclusions * emerge from these facts:

(i) From the observed bond distances the linkages between unlike atoms cannot be resonance hybrids involving ideal ionic and ideal covalent structures, both types possessing longer distances.

(ii) There is no continuous transition from the ideal to the actual covalent linkage (with shorter distances) and finally to the ideal ionic linkage (with longer distances). This indicates that there is a principal difference between the ideal ionic linkage and the covalent linkage, which may possess a more or less polar character.

The polar character of covalent linkages, which is mainly responsible for the shortening of the bond distances and the increase of bond energies, cannot be interpreted in terms of ideal ionic structures, e.g. by resonance involving such structures and hypothetical resonance energies. It only indicates that in addition to covalent forces (as, e.g., in the H₂ molecule), forces of the same type as are responsible for an ideal ionic linkage, namely Coulomb forces (in addition to other possible forces), will contribute to the bond energy as well as influence the bond distance.

Qualitatively, the difference between these two interpretations may be thus described: Resonance between ideal ionic and covalent structures presupposes that the electrons responsible for the actual covalent linkage will vibrate between these two extreme states, their relative fictitious "lifetimes" being essentially dependent on their relative stability. The given interpretation assumes that the average distribution of the electrons will at no time appreciably deviate from the actual equilibrium state. The former supposition also involves the assumption that superposition of different forces, possibly expressed by different structures, is accompanied by an energy gain, the resonance energy; the latter that the superposition of different forces may be additive. This interpretation is essentially in agreement with the generally accepted ideas of chemistry before the hypothesis of resonance and similar speculations influenced by the limitations of the present theoretical methods were introduced.

The original conclusion that the ionic character of a linkage has no influence on the bond length was erroneous (*cf.* above). It necessitated an explanation of the deviations of the observed bond distances from those calculated with the original atomic radii in the case of linkages between halogen atoms and atoms of the second and lower rows of the periodic table such as Sn, Ge, Sn, P, As, Sb, S, Se, Te. These linkages have been interpreted by complicated hybrids of resonance structures involving double bonds.¹⁵ Thus, in the case of SnCl₄ structures with negatively charged Si ions such as Cl₄Si⁻ - Cl⁺; Cl₄Si⁻ (- Cl⁺)₂; Cl₄Si⁻ (- Cl⁺)₃

¹² *Loc. cit.*, p. 171.

¹⁴ *Loc. cit.*, p. 346.

* Allowance for appreciable variations of the ideal ionic radii can be made without detriment to these conclusions.

$\text{Si}^{++} (\text{Cl}^-)_4$ should contribute. The hybrid for SiF_4 should also contain structures with partial triple bond character of the silicon-fluorine linkage and two positive charges on the fluorine atom $\text{F}_2 \text{Si}^{++} \text{F}^{\prime\prime}$.

The new atomic radii and the recognition that the ionic character of the bonds has an appreciable effect on their distances removes the necessity for these speculations, which introduce most improbable structures with Cl^+ and F^- ions possessing one and even two positive charges and Si ions with one, two, three and even four negative charges. These halides do not behave differently from the halides of the first row elements and other linkages.

It is true that the shortening of the interatomic distances of these halides does not always concur with their electronegativity differences (cf. Table V), but similar "anomalies" are also observed for the hydrogen halides and other linkages involving a H atom, where complicated unlikely structures as shown above are not possible.

Whereas the shortening of the bond distances within these halides, e.g. SnCl_4 and SnF_4 , has been attributed to resonance involving 50 % and more double bond character of the linkages,¹⁶ and their ionic character has been considered to be of little or no importance, the increase of the bond energy has been attributed to 30 and 70 % ionic character of the linkage,¹⁷ the double bond character being apparently without any influence on the bond energy. This is inconsistent and unlikely. The shortening of the bond distances and the increase of the bond energies are known to be related phenomena and are, obviously, due mainly to the same cause.

Pauling and Huggins have attributed to the boron atom a covalent radius 0.88 Å., which was obtained by extrapolation from those of the other first row atoms C, N, O, F. The observed distances of the $\text{B}-\text{C}$, $\text{B}-\text{F}$, $\text{B}-\text{Cl}$, $\text{B}-\text{Br}$ linkages within BMe_3 , BF_3 , BCl_3 , BBr_3 , the distances calculated with the original ideal atomic radii, and their differences are given in Table IV. The shortening (Δ) of the $\text{C}-\text{B}$ distance by 0.09 Å. has been attributed to the incompleteness (sextett) of the B valency shell,¹⁸ the additional shortening of the boron-halogen linkages by 0.03, 0.04, and 0.06 Å. to resonance between structure, BX_3 , the three structures $X_2\text{B}^- - X^4$ involving linkages with double bond character, and, in order to overcome the unfavourable distribution of charge, the structures $X_2\text{B}^+X^-$ and $X^- \text{BX}^+X^+$.

The revised atomic radii of the first row elements also necessitate the revision of the boron radius. Bauer and Beach¹⁹ suggest 0.85 Å., the author proposes the still lower value 0.82 Å., which is in better agreement with an extrapolation from the other first row elements and the observed elementary interatomic distance²⁰ of $\text{B}-\text{B}$. The distances calculated with the revised atomic radii and their deviations (Δ') from the observed distances are also shown in Table IV.

It is unnecessary to assume either the existence of resonance between such unlikely structures, or the effect of the incomplete shell of the B atom on the bond distances. In agreement with the almost identical electronegativities (2.0 and 2.1 respectively) of B and H, the shortening of the B linkages is similar to that of the corresponding H linkages (cf. Table V). This not only excludes the suggested original explanations, since they are not applicable to the H linkages, but also strongly supports

¹⁵ Loc. cit. 1, p. 228.

¹⁶ Loc. cit. 1, p. 230.

¹⁷ Loc. cit. 1, p. 74.

¹⁸ Loc. cit. 1, p. 170; Lévy and Brockway, *J. Am. Chem. Soc.*, 1937, **59**, 2085.

¹⁹ Loc. cit. 1, p. 237.

²⁰ *J. Am. Chem. Soc.*, 1941, **63**, 1394.

²¹ Douglas and Herzberg, *Physik. Rev.*, 1940, **57**, 752.

²² For literature, compare refs. 1 and 10; Herzberg, *Molecular Spectra and Molecular Structure*, I, New York, 1939.

²³ For literature, compare refs. 1 and 10; Maxwell, *J. Optical Soc. Am.*, 1940, **30**, 375; Lister and Sutton, *Trans. Faraday Soc.*, 1941, **37**, 406.

the conclusion that the polar character of the covalent linkages is to a great extent responsible for their observed shortening.

Summary.

There is a principal distinction between the ideal ionic linkage and the covalent linkage which can possess to a varying degree a polar character. An analysis of the observed bond energies, and bond distances of covalent linkages indicates that their stability will be due to (i) the fundamental covalent forces; (ii) ionic, *i.e.* Coulomb forces; (iii) other forces, *e.g.* those connected with the deformation of the electrons and nuclei.

The actual state of these linkages cannot be described in terms of ideal classical structures, *e.g.* as resonance hybrids between ideal covalent and ideal ionic linkages (structures) or structures involving double bonds. Such an interpretation of covalent linkages, being a working hypothesis, which would allow the extrapolation of their bond properties from those of idealised classical structures, is inconsistent with the observed bond energies and bond distances.

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REVIEWS OF BOOKS.

Benjamin Franklin's Experiments. A new edition of Franklin's Experiments and Observations on Electricity. Edited, with a Critical and Historical Introduction, by I. Bernard Cohen. (Harvard University Press. Milford, Oxford University Press, 1941. Pp. xxviii + 453. Price 22s. od. net.)

There are few more intriguing figures in the story of eighteenth-century science than that of Benjamin Franklin. Not that his character was complex; on the contrary, it is the combination of simplicity and shrewdness, of intellectual curiosity with downright honesty and devastating common sense, which gives to Franklin's character so much that is profoundly interesting. And to these personal qualities, added zest is given by the almost romantic details of the life-story of the printer's apprentice who, in the fullness of time, became Minister Plenipotentiary to the Court of France, and later, President of the Executive Council of Pennsylvania.

His long life (1706-1790) almost encompassed the century and witnessed changes which, even in our days of changing outlook, may fairly be described as unexampled in magnitude. The political world into which he was born was one in which the Divine Right of Kings was a commonplace, even though it had been successfully challenged in Britain; when he died, the Industrial Revolution was well under way, and our modern political structures were taking shape. The scientific world of 1706 was still, despite the nineteen-year-old *Principia*, swimming in the whirlpool of the Cartesian vortices; in 1790, the mechanical outlook of the Newtonian philosophy was firmly established. And in the bringing about of these vast changes, Franklin with literal truth could have said, *pars magna fui*.

His contributions to the advancement of electrical science are too well known to need recital; fully to appreciate the ingenuity and simple directness of Franklin's attack, his experiments should be read in the

original accounts, now happily very easy of access in the admirable edition under review. What is not so well known is that, following the revolt of the American colonies, Franklin's discoveries were disparaged, and, in particular, it was argued that rounded ends were better suited to lightning conductors than the points advocated by Franklin. "George III, on its being proposed to substitute knobs instead of points, requested that Sir John Pringle (the President of the Royal Society) would likewise advocate their introduction. The latter hinted that the laws of nature were unalterable at royal pleasure; whereupon it was intimated to him that a president of the Royal Society entertaining such an opinion ought to resign, and he resigned accordingly" (*Penny Cyclopaedia*, art. *Pringle, John*).

The editor of this volume has accomplished—not completed, be it noted—a piece of work which has earned for him the grateful thanks of all who are interested in the history of science; he has enhanced the value of his scholarly edition by a number of introductory chapters and appendices dealing with Franklin and Science, Electricity before Franklin (an admirable survey), Franklin's Work in Electricity, the Editions of Franklin's Book and the Lectures and Discoveries of Franklin's Collaborator—Ebenezer Kinnersley.

We say "not completed" advisedly; for the editor has whetted our appetite, and we look to him for a second volume which shall contain an account of Franklin's other contributions to science, and yet another volume which shall contain the autobiography, and a selection of Franklin's essays and of his political and personal correspondence; the student of Franklin will then indeed be well equipped.

A. F.

War Gases, Their Identification and Decontamination. By MORRIS W. JACOBS. Interscience Publishers, Inc., New York, 1942. Pp. 180 + xiii. Price \$3. (Available through Imperial Book Co. Ltd., London.)

There are few war hazards where proper action on the slogan "Be prepared" is so effective as with war gases. Insidious possibilities for the many can be enormously reduced by measures taken by the few, if each does his share. The many are provided with gas masks and have little to do save to keep them in good order, to wear them if necessary, and to follow simple directions; the few require to have specialised knowledge and this book is written for them.

During the last war about 3000 chemical substances were investigated to determine their value as war gases, but of these only 38 were actually used in the field, and only 6 were of importance. Almost all those used had for long been recognised as potentially toxic materials. Because of the rigid requirements of a chemical warfare agent, experts consider it unlikely that a completely new material could be developed at short notice and at the same time be kept secret.

The properties of the potential war gases are well known and have been described in standard works, such as those of Prentiss and of Sartori, and further information is spread throughout scientific literature. The author has selected the essentials from such sources and has incorporated the information published in this country by the Ministry of Home Security

and by the Ministry of Food, and in America by the United States War Department and by the Office of Civilian Defense.

The preface states that the book can be used for the training of gas identification officers, as a manual for chemists and decontamination officers, and as a source of information on the analytical chemistry of the war gases. It is probable, however, that Gas Identification Officers and Decontamination Officers of the Civil Defence will find the book outside their scope and that they will be better served by the official publications specially prepared for their use; but chemists concerned with the specific identification of gases not readily recognised by Gas Identification Officers, and that larger body of chemists who might be called upon to deal with contaminated materials, particularly food, will find just what they need. The book covers detection, sampling and identification of chemical warfare agents, and gives descriptions of measures which may be taken for the decontamination of affected areas and materials.

The volume is compact, concise and well arranged. No one can forecast all the possibilities which might arise if aircraft and gas warfare are associated; but any chemist who might be concerned professionally with such possibilities cannot afford to be without this book, although it is hoped he will never need to use it.

J. R. N.

DISTRIBUTION EQUILIBRIA IN THE SYSTEM TIN-STANNOUS SULPHIDE.

BY J. S. ANDERSON AND M. J. RIDGE.

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Distribution equilibria in systems involving a fused metal and a molten metallic sulphide present a number of features of theoretical interest. Equilibria between metal and matte are frequently encountered in the processes of non-ferrous metallurgy, and the factors that determine the distribution of minor constituents of such systems are directly relevant to the problem of recovering and extracting certain of the rarer elements as by-products of the treatment of base metal ores.

Little quantitative work appears to have been done on this topic. W. and I. Noddack made some observations relevant to the geochemistry of Re,¹ and more recently Noddack, Noddack and Bohnstedt² have determined distribution coefficients of Mo, Ru and the platinum metals between Fe and FeS. The qualitative correlation between the geochemical distribution of the elements and their "siderophile" or "chalcophile" tendencies had already been pointed out by Goldschmidt.³ From the nature of the phase equilibria in the system Fe--FeS, all these studies are concerned with partition between the solid and the residual liquid phases; this introduces a number of extra factors that complicate any theoretical discussion of the results. The fullest investigation of distribution equilibria in the liquid state is to be found in the work of Guertler and Maisner⁴ on ternary systems of Cu, S, and a second metal (Pb, Sn, Sb and Bi). This was primarily directed, however, towards a study of the solid phases crystallising from the melt, and it affords little quantitative information as to the composition of the co-existing liquid phases.

The system Sn—SnS⁵ is particularly suited to the study of distribution equilibria in a well-defined metal-metal sulphide system with two liquid phases. Stannous sulphide is relatively fusible (m.p. 870°), and two liquid phases are present at temperatures above 858° in mixtures containing between 10 % and 90 % of SnS. This is convenient experimentally, since the system can be investigated in sealed silica vessels, whereas the systems Cu--Cu₂S employed by Tammann and Bohner⁶ and by Guertler and Maisner,⁷ and Fe—FeS^{1, 8} introduce a variety of difficulties owing to the higher temperatures required. The metals added as third component were selected from among the heavy metals with a view to the variation of such factors as valency, heat of formation of the sulphide, etc., that might have an influence on the distribution equilibrium. We report here only the results obtained for the distribution of Cu, Ag, and Pb, for which fairly complete data are available.

Experimental.

Materials.—A commercial refined tin of good quality, assaying about 99.85 % Sn, was used for the metallic phase, and for the preparation of SnS. The added constituents were electrolytic Cu, pure assay Pb and

¹ W. and I. Noddack, *Z. physik. Chem. A*, 1931, 154, 207.

² W. and I. Noddack and Bohnstedt, *Z. anorg. allg. Chem.*, 1940, 244, 252.

³ Goldschmidt, *J. Chem. Soc.*, 1937, 655.

⁴ Guertler and Maisner, *Metall. Ber.*, 1921, 18, 145.

⁵ Anderson and Ridge, *Trans. Faraday Soc.*, 1943, 259, 98.

⁶ Tammann and Bohner, *Z. anorg. alg. Chem.*, 1924, 135, 161.

assay Ag. Stannous sulphide was made by the direct combination of Sn with redistilled Merck S, and sulphides of the other metals were prepared by a similar process.

Distribution Experiments. About 3 g. of metallic Sn and 5 g. of SnS were taken in each experiment, so as to give approximately equal volumes of the two liquid phases. These, together with an appropriate weighed quantity of the added constituent, either in the form of free metal or as sulphide, were introduced into a silica test tube, which was then constricted, evacuated with a rotary oil pump, and sealed off at the constriction. All experiments were carried out at the one temperature, $910^{\circ}\text{C}.$, to which the furnace was held by hand regulation. Calculation of the "theoretical" distribution coefficients (see below) shows that the equilibria are unlikely to be strongly dependent upon the temperature.

In each experiment, two tubes were filled with mixtures of approximately the same gross composition. In one the added constituent was originally present as metal, and in the other it was added as sulphide. The equilibrium was thus approached from each direction in every experiment. The two tubes were heated in the rocking furnace⁶ at 910° for 8 hours and the furnace was then tilted to the upright position. After $\frac{1}{2}$ hour, the tubes were dropped through the bottom of the furnace into cold water. Rapid quenching ensued, resulting in very fine grained ingots. This latter was desirable, not only in order to avoid any change in composition and segregation of the components during crystallisation, but also because in coarser specimens the softness and friability of SnS, as compared with the matrix of Sn, was found to lead to preferential loss of SnS during sampling, and therefore to analytical errors. The sulphide phase appeared to wet the tube and to form a thin skin around the quenched ingot. This skin was first removed, and then a polished section was worked upon the ingot so that the structure and separation of the two layers could be examined. From each layer, a 2 g. sample, free from prills, was taken for analysis.

The accurate determination of Ag, Pb and Cu in metallic Sn or SnS is somewhat troublesome. The method finally adopted was considerably modified from the Freiberg assay method as given by Lunge-Berl,⁷ and in outline was as follows. Numerous blanks showed that it gave a quantitative recovery of 5 mg. of any of these metals, present either singly or together, in a 2 g. sample of tin.

The sample (2 g.) was dissolved in nitric-hydrochloric acid (30 ml. of 1 : 2 mixture). The solution was diluted, neutralised with ammonia, and treated with a concentrated solution of 15 g. of tartaric acid. Addition of ammonia then dissolved up AgCl, and yielded a clear alkaline solution from which CuS, PbS and Ag₂S were quantitatively precipitated by sodium sulphide; addition of filter paper pulp at this stage was advantageous. Co-precipitated SnS was removed, and the precipitate washed chloride-free, by dilute Na₂S solution. The filter was destroyed by digestion with H₂SO₄, HNO₃. On dilution and addition of alcohol, Pb, if present, was obtained as PbSO₄. From the solution (or filtrate from the PbSO₄) Ag was precipitated by means of HCl, and Cu was ultimately precipitated as CuCNS.

Results and Discussion.

The results are collected in Tables I and II; the brackets indicate the pairs of tubes heated simultaneously, as described above. The distribution coefficients C_s/C_m , calculated from the ratio of columns 1 and 2, show a certain amount of unsystematic scattering, as is usual in studies of this type, and are therefore not tabulated for each experiment. The scattering is probably attributable chiefly to imperfect separation of the

⁶ *Chemisch-technische Untersuchungsmethoden*, 7th ed., II, 420.

two liquid phases, since the deviations are larger than could be accounted for by analytical errors, and are clearly not due to incomplete attainment of equilibrium. Macroscopic prills of the conjugate phase were avoided by the sampling procedure described. The tendency for emulsification in systems of this type is strong, however (*cf.* refs. ³ and ⁴), and any microscopic admixture of the two phases may well have escaped detection. The interfacial tension between Sn and SnS appears to be sensitive to the composition of the melt; in experiments on the distribu-

TABLE I *

Concentration—Weight %.	
In Metal Phase <i>C_m</i> .	In Sulphide Phase <i>C_s</i> .

Distribution of Lead.

%	%
{ 0.52	{ 0.39
1.14	0.97
{ 1.89	{ 1.70
2.01	1.47
{ 3.62	{ 2.68
4.89	3.52

Distribution of Silver.

%	%
{ 1.02	{ 0.24
1.67	0.47
{ 2.51	{ 0.60
2.93	0.88
6.83	1.93
9.35	1.95
{ 16.60	{ 4.84
17.25	4.13

TABLE II *

Distribution of Copper.

<i>C_m</i> .	<i>C_s</i> .	<i>K'</i> .
%	%	
{ 0.43	{ 0.82	0.167
0.67	1.40	0.167
1.26	2.28	0.165
{ 1.70	{ 4.65	0.164
2.50	6.12	0.167
2.28	5.12	0.168
2.72	7.86	0.162
{ 6.28	{ 12.03	0.164
10.57	11.06	0.162

* In columns 1 and 2 figures in roman type refer to concentrations wherein equilibrium is approached from metal, and those in italics approached from sulphide.

tion of Bi (not reported), the separation of the phases was so incomplete as to render the results valueless. The experimental data are best evaluated by plotting them as in Fig. 1, whence the distribution coefficients may be calculated from the slope of the smoothed curves.

We may regard the distribution as determined, in the first place, by the chemical equilibrium in the generalised reaction



If X_s , X_m be the mole fractions of MS and M in the sulphide phase and metallic phase respectively, then according to the simple mass action law,

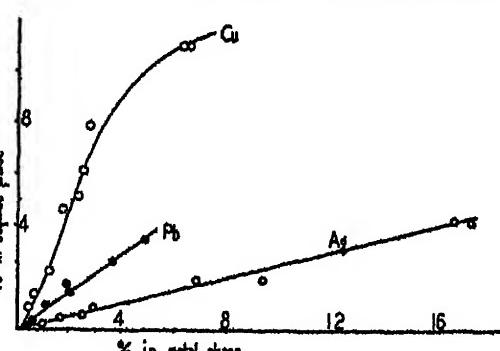


FIG. 1.

$$\frac{X_s(1 - X_m)}{X_m(1 - X_s)} = K \quad \dots \quad \dots \quad \dots \quad (2)$$

In dilute mixtures ($1 - X_s$, $1 - X_m$ tending towards unity),

$$X_s/X_m = K$$

and the equilibrium constant or distribution coefficient can be equated to the limiting slope of the (not quite linear) plot of X_p against X_m . In such a condensed system, the simple mass action law is not likely to be valid over any wide range of composition, and the Lorenz equilibrium law^a is more strictly applicable. This can be simplified to the form^b $K' = K e^{\alpha K}$, where K is the simple mass action constant. However, as Fig. 1 shows, the distribution curve for Pb and Ag are very nearly linear, so that the coefficient α in the above expression is small enough to neglect for these cases. For Cu, the distribution curve is not linear, and its form closely resembles the curves found by Lorenz and his co-workers to describe the equilibria in metal-fused salt systems. The results do, in fact, accord very satisfactorily with the modified Lorenz expression $K' \approx K e^{-0.05K}$. The constancy of the product (Table II, column 3) is admittedly not very sensitive to small changes in the coefficient α . Equilibrium constants derived from the limiting slope of the curves of Fig. 1, including that for copper are given in Table III.

The results for Ag and Cu raise several issues. In the first place, the displacement equations—e.g.



would require that the equilibrium constant in these systems should be given by the expressions $\frac{[\text{Cu}]}{[\text{Cu}]_m} \cdot \frac{[\text{Ag}]}{[\text{Ag}]_m}$ respectively, whereas for Ag it is found that $[\text{Ag}]_m/[\text{Ag}]_l$ is a very good constant. The corresponding quotient for Cu is not itself a constant, but varies systematically according to the Lorenz law. In neither case are the experimental data compatible with equation (3). It follows that Cu and Ag must be present in both phases not as Ag and Ag_2S , Cu and Cu_2S respectively, but in molecular units of similar complexity. A number of possibilities present themselves in explanation of this fact.

(a) The two liquids are not pure Sn and pure SnS, but the conjugate liquids of composition $\text{Sn} + 0.092 \text{SnS}$, $\text{SnS} + 0.099 \text{Sn}$. In the dilute systems studied, the added metal is not in excess of the amount that could be combined, as Cu_2S and Ag_2S , with the S present in the metallic phase; the sulphides might then undergo a simple partition equilibrium. However, both this and the converse hypothesis (that both are dissolved as metal in the sulphide phase) can be eliminated, since the distribution of Cu and of Ag trend in opposite directions, Cu having a greater, and Ag a lesser affinity for S than has Sn.

(b) Copper could conceivably react with SnS to form Cu_2S , although at the temperature of the experiments, and in a liquid containing an excess of metallic Sn, that is improbable. Moreover, such an hypothesis cannot be extended to explain the data for Ag.

(c) Copper and Ag may be present in the sulphide phase predominantly in the form of compounds (e.g. complex sulphides) containing one atom of Cu or Ag in the radicle. This is a possibility that has to be taken into account. In the solid state, both Cu_2S and Ag_2S are semimetallic; mixed conductors at low temperatures, but ionic conductors in their high temperature modifications. In the fused state, according to Savelsburg,^c pure Cu_2S is again an electronic conductor. On addition of other metallic sulphides, however—e.g. Na_2S or FeS , but not NiS —electrolytic conducting properties are developed; the Cu is then combined in a complex anion, for which positive evidence was obtained from transport experiments. It may well be that, in dilute solution in SnS, the Cu_2S is converted largely or quantitatively to such complex sulphides. Whether such an explana-

^a Lorenz and others, *Z. anorg. allg. Chem.*, 1924, 138, 285; 1925, 145, 239; 1925, 150, 99, 343; 1926, 162, 314.

^b Jander and Rothschild, *ibid.*, 1928, 172, 129.
^c Savelsburg, *Z. Elektrochemie*, 1940, 46, 379.

tion is equally valid for Ag_2S can only be conjectured. The converse process—association in the metal phase—is an alternative possibility, since both Cu and Ag form intermetallic compounds with Sn. The persistence of intermetallic compounds in the melt is a matter open to discussion. However, if we regard the liquid as a disordered lattice structure, it seems probable that there will be some short-distance order persisting over a wide range of temperature. At the concentrations found in our experiments this could not, however, correspond to any compound richer in Ag or Cu than the 1 : 1 compound, and intermetallic compound formation is unlikely to be a disturbing factor.

(d) As stated above, the distribution is set up between liquids of the composition $\text{Sn} + 0.0092 \text{ SnS}$ and $\text{SnS} + 0.099 \text{ Sn}$ respectively. It is an interesting question whether these liquids are more closely related to the pyrosols, formed by dispersion of metals in ionic melts, or whether they are the liquid analogues of the non-stoichiometric crystalline phases so characteristic of the sulphides of the heavy metals, in which the valency forces are homopolar or semimetallic in character. There would then be no rigidly fixed ratio between atoms and valency electrons, and atom-for-atom replacement of Sn by a univalent metal (Ag or Cu) would be quite possible. It may be that the distinction between the last two hypotheses is somewhat arbitrary, turning upon how far a complex ion in the melt is a persistent entity, and how far complex formation is transient, with a purely statistical existence.

In the light of the foregoing discussion it is of interest to see how far the distribution equilibria are fixed by the thermochemistry of the displacement reaction (1). Tammann and Bohner,⁶ from observations on the effect of adding Mn or Al to the system Cu—Fe—Cu₂S—FeS, concluded that all metals, the sulphides of which had a larger exothermic heat of formation than FeS, would be concentrated in the sulphide phase. This is essentially only an application of the Berthelot-Thonissen principle, and in view of the factors already discussed it is not surprising to find that it is not always even qualitatively correct.

Thermochemical data for the heavy metal sulphides are scanty, and latent heats of fusion are lacking. The heats of formation of PbS and Cu₂S are known with sufficient accuracy; for Ag₂S, the value determined electrometrically by Kapustinsky and Makolkin¹¹ is probably more reliable than that cited by Bichowski and Rossini.¹² For SnS, however, there is wide discrepancy between published values. Jellinek and Zakowsky,¹³ from measurements of the reduction equilibrium of SnS with hydrogen found $\Delta H^{\circ} = -22.7$ K.cal., whereas Kapustinsky and Makolkin¹¹ obtained $\Delta H^{\circ} = -18.2$ K.cal. The latter is probably the more trustworthy figure, but the uncertainty is sufficient to reverse the qualitative interpretation of our results for the distribution of Cu and Pb. In the absence of other necessary data, the heat of reaction for equation (1) at the temperature of reaction (1183° K.) cannot be found; as specific heats and latent heats in systems of this type are likely to cancel out between reactants and resultants, it is not likely to differ, in sign at least, from that calculated using the values for ΔH° . Britzke and Kapustinsky¹⁴ have, however, determined from reduction equilibria the free energy change for the reaction $2\text{M} + \text{S}_8 = 2\text{MS}$ for a number of metals, and their values for ΔA° are included in Table III.

Though still referring to a temperature below that of our experiments, we may use the free energy data to calculate an approximate equilibrium constant for the displacement reaction (1). For Pb, this leads to an "ideal" value X_s/X_m of about 2, whereas the Pb is actually concentrated

¹¹ Kapustinsky and Makolkin, *Acta Physicochim.*, 1939, 10, 245.

¹² *Thermochemistry of Chemical Substances*, Chemical Catalog Co.

¹³ Jellinek and Zakowsky, *Z. anorg. allg. Chem.*, 1925, 143, 1.

¹⁴ Britzke and Kapustinsky, *Z. anorg. Chem.*, 1933, 213, 71.

slightly in the metallic phase. If the thermochemical data for SnS are low (see above), the discrepancy is merely transferred from the Pb to the Cu : one or other of these metals must be distributed contrary to the free energy change in the displacement reaction. Moreover, inspection of Goldschmidt's classification of the metals according to their distribution between Fe and FeS shows that similar discrepancies exist in several instances in that system also. It appears to us that this observation is to be closely linked up with the problem of the constitution of the fused sulphides.

TABLE III

Compound.	$C_{\text{Cu}}/C_{\text{m obs.}}$	$X_{\text{Ag}}/X_{\text{m obs.}}$	$Q_F^{298^\circ}$ (k.cal.)	A^{1400° (k.cal.)
SnS	—	—	18·2	16·8
PbS	0·70	0·06	22·4	17·6
Cu ₂ S	1·85	2·25	18·5	23·1
Ag ₂ S	0·26	0·32	7·5	15·0

Calculations of the ideal distribution coefficient for Ag and Cu have no great significance in view of the facts discussed in an earlier section. It may be noted, however, that for Ag, at least, the partition is more uniform than would be anticipated from the difference in free energies of SnS and Ag₂S. Whether this is an additional indication of some association in the sulphide phase is uncertain. It may be recalled, however, that Jander¹⁸ found Au to be distributed far more uniformly between Fe or Ag and fused silicates than would be expected from thermodynamic calculations, pointing to a true atomic solution in the non-metallic liquid phase, in addition to the chemical equilibrium.

Summary.

The distribution of Cu, Ag and Pb, present in low total concentration, between the two liquid phases in the system Sn—SnS has been studied at 910°. Lead is slightly, and Ag strongly concentrated in the metallic phase, while Cu is concentrated preferentially in the sulphide phase. The direction and magnitude of the distribution coefficient in such systems is not determined solely by the thermochemistry of the displacement reaction



The results are discussed with reference to the constitution of metallic sulphides in the fused state.

¹⁸ Jander, *Z. anorg. allg. Chem.*, 1945, 143, 377.

THE SYSTEM TIN-STANNOUS SULPHIDE.

By J. S. ANDERSON AND M. J. RIDGE.

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The semi-metallic nature of the metallic chalcogenides is shown not only by the optical and electrical properties of the crystalline solids, but also by the considerable degree of miscibility with metals in the fused state. The metallic character diminishes in the series tellurides > selenides > sulphides, and whilst the miscibility of the heavy metals with their fused sulphides is, in a number of cases, complete (e.g., Ni—FeS,¹

¹ Loebe and Becker, *Z. anorg. allg. Chem.*, 1912, 77, 301.

Co—CoS,² Bi—Bi₂S₃,³ etc.), it can be inferred from the abnormal inflection displayed by the liquidus curve that the melt deviates widely in properties, in every instance, from an ideal liquid mixture. In some systems (Cu—Cu₂S,⁴ Sb—Sb₂S₃,⁵ etc.) the formation of two liquid phases has been observed.

In examining the published data concerning systems suitable for the study of distribution equilibria,⁶ we observed that the abnormality in the phase diagram of the system Sn—SnS,^{7,8} is so pronounced as to indicate that there must be a wide range of immiscibility. This possibility seems to have been considered, and explicitly rejected, by Biltz and Mecklenburg although the almost horizontal portion of their fusion curve points strongly in this direction. Further, having regard to the wide interval between the boiling points of metallic tin (2300°) and of stannous sulphide (1240°), the course of their boiling point curve is compatible only with the evaporation of stannous sulphide from a phase of constant composition—the sulphide phase of a conjugate pair of liquids.

This conclusion was at once confirmed by an experiment of the type described below. The flat portion of Biltz and Mecklenburg's melting point curve marks the range of composition over which two liquid phases, approximating in nature to metallic Sn and SnS respectively, coexist in the melt. We have accordingly investigated the composition of the conjugate liquid phases at a number of temperatures between the melting point and 1200°. The main features of Biltz and Mecklenburg's phase diagram are consistent with all our observations, and we have not, therefore, re-examined the solid-liquid equilibrium as a whole. We have, however, made some observations relevant to the tin-rich corner of the diagram, which presents some features common to systems of this type.

Experimental.

The tin used in this work was a high grade commercial refined tin, assaying better than 99.85 % Sn. Stannous sulphide was prepared from the same sample by direct combination with redistilled Merck sulphur. Tin, with about twice the requisite quantity of S, was placed in a long Pyrex test tube. The S was heated to boiling, whereupon the temperature of the Sn was raised until vigorous combination took place with the refluxing S. The S vapour protected the SnS from ingress of air, while the condensation of S on the surface of the SnS prevented oxidation from occurring when the tube was cooled after completion of the reaction. The highly crystalline product was crushed to pass a 100-mesh sieve; it approximated closely to the composition SnS, but contained a slight excess of S.

(A) The Conjugate Liquid System.

5 g. of metallic Sn and 5 g. of SnS were introduced into a silica tube, which was then constricted, evacuated with a Hyvac pump, and sealed off at the constriction. The sealed tubes so filled were heated in an electric furnace arranged so that it could be rocked about a pivot, after the manner adopted by Lorenz in his studies of fused salt systems.⁹ Each tube was agitated for three hours at the selected temperature. The furnace was tilted into an upright position, and the contents of the tube were

² Friedrich, *Metallurgie*, 1908, 5, 212.

³ Aton, *Z. anorg. allg. Chemie*, 1905, 47, 387.

⁴ Heyn and Bauer, *Metallurgie*, 1906, 3, 76.

⁵ Chretien and Guinchard, *Z. anorg. allg. Chemie*, 1912, 78, 245.

⁶ Anderson and Ridge, *Trans. Faraday Soc.*, 1943, 259, 93.

⁷ Pelabon, *Compt. rend.*, 1906, 142, 1147.

⁸ Biltz and Mecklenburg, *Z. anorg. allg. Chemie*, 1909, 64, 226.

⁹ Lorenz, Fraenkel and Silberstein, *ibid.*, 1923, 131, 247.

allowed to settle for at least an hour, at the same temperature. The tube was then dropped through the bottom of the furnace into cold water, and quenched practically instantaneously.

The resulting ingot was made up, in every case, of two layers, clearly indicating the existence of two liquid phases at the moment of quenching - a lower tin rich phase, and an upper, specifically lighter sulphide phase. In a polished section, under moderate magnification, it could be seen that the metallic layer contained needle-like crystals of SnS. Hence the metallic liquid of the melt contains dissolved SnS, which is thrown out of solution on solidification. Micrographic examination of the sulphide phase similarly showed it to consist of soft, crystalline SnS in a matrix of metallic Sn. The separation of the two phases was not perfect, even after settling for an hour; there is a distinct tendency for emulsification at the interface, and the density difference is probably not high enough to bring about a rapid separation. By sectioning and polishing each ingot it was possible to select for analysis a 2 g. sample of each phase, quite free from visible prills. Except for the region of the interface, where prills were obvious, the micrographic examination showed that each layer was homogeneous in composition throughout (*cf.* ref. 8).

Analysis.—It was found that the best analytical precision was achieved by determining the S content of each phase. Determination of Sn by direct ignition to SnO_2 , as adopted by Biltz and Mecklenburg, led to somewhat variable results, due probably to the perceptible volatility of SnS. For

analysis, an appropriate weight of material (0.3 g. of sulphide phase, 1 g. of metal phase) was treated with HCl. The H_2S evolved was carried over on a stream of CO_2 into Br water, and the resulting $\text{H}_2\text{S}(\text{C})_4$ was determined as BaSO_4 .

TABLE I

Temperature.	% S in Metal Phase.	% S in Sulphide Phase.
900°	2.23	19.74
980°	2.27	19.73
1080°	2.27	19.91
1180°	2.52	19.65

Experiments following the procedure described were carried out at temperatures of 900°, 980°, 1080°, and 1180°, with results recorded in Table I. The mutual solubility of Sn and SnS changes very little over the temperature range examined, though the increase of miscibility apparent at 1180° is probably real.

(B) The Solidification Curve of Tin-Rich Mixtures.

The earlier investigations ^{7, 8} did not include any freezing point measurements on mixtures containing less than 3.2% of S. The arrest at 232°, observed over a wide range of composition, points to the formation of a eutectic that differs very little in composition from pure Sn. It is evident from the points now fixed in the phase diagram that the arm AB (Fig. 1) of the freezing curve of the metallic liquid phase must ascend too steeply to be traced readily by thermal analysis alone.

To fix one or more points on this part of the diagram, we carried out a few experiments as follows. Mixtures were made up to contain a known low concentration of S, either (a) by sealing up weighed quantities of Sn and S, or (b) more conveniently, by mixing weighed quantities of Sn and the tin-rich phase from equilibrium experiments at 90°. The tubes were heated at temperatures high enough to ensure complete fusion of the contents to a single liquid phase. The temperature was lowered to a predetermined value T_s , and the tube was left in the furnace at that temperature for an hour. It was then quenched, and the ingot was

sectioned and polished. If the temperature T_e were within the two-phase region, the growth of long prismatic crystals of SnS was apparent, while ingots quenched from above the temperature of primary crystallisation had an extremely fine-grained structure. The results are summarised in Table II. Current events made it impossible to pursue this part of the work further. It is clear that primary crystallisation of a mixture containing 0.50 % S commences below 700°, but above 600°.

To examine further the question of the eutectic composition, a very careful metallographic examination was made of a mixture, containing 0.50 % S, which had been cooled as slowly as possible within the furnace. The ingot was sectioned and polished, and then progressively etched with acid alcoholic FeCl₃, as recommended for the metallographic examination of Sn samples.¹⁰ So treated, the primary crystallisation of SnS from the melt yielded crystals of large size, embedded in an apparently homogeneous matrix of tin. Even under the highest magnification no certain evidence of a eutectic structure was found. There was some indefinite structure visible, but having regard to the fact that only a commercial refined tin was available for the work, we are inclined to attribute this to coring, produced by the 0.1-0.15 % of metallic impurities. Practically all the S must have been present in the SnS crystals, with very little indeed in the eutectic.

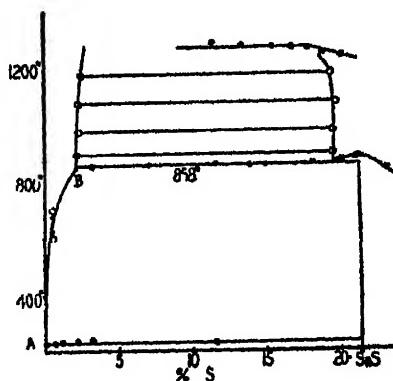


FIG. 1.
Open circles: experimental points from this work.
Solid circles: data of Blitz and Mecklenburg.

TABLE II

Composition of Melt.	T_e .	Character of Polished Section.
1.50 % S	600°	Duplex, much SnS crystallised.
0.50 % S	800°	No detectable crystallisation of SnS.
0.50 % S	700°	No detectable crystallisation of SnS.
0.50 % S	600°	Duplex.

Discussion.

The extremely low concentration of SnS in the eutectic is a feature paralleled in other metal-chalcogen systems in which there is a wide difference in melting point between the metal and its chalcogenides. It is a consequence of the extreme non-ideality of such liquid mixtures, and is thus directly associated with the same cause as the partial miscibility of the liquid phases. For one such system, that of Pb with S, a study of extremely dilute alloys has been made by Greenwood and Worner,¹¹ who found that the eutectic contained less than 0.0006 atoms per cent S (= 0.009 weight per cent.). There is, indeed, a close similarity between

¹⁰ Internat. Tin Research and Development Council, Tech. Publ., Series A, No. 47, p. 9.

¹¹ Greenwood and Worner, *J. Inst. Metals*, 1939, 6, 854.

the systems Sn—SnS, Pb—PbS, so far as the phase diagram of the latter is known. Friedrich and Leroux¹² did not, indeed, notice any two-phase liquid region in the latter system, but Guertler and Meissner¹³ found that mixtures containing between 5 % and 10 % of S separated into two layers. The miscibility of Sn with SnS is thus distinctly less than that of Pb and PbS, so that the actual eutectic composition in the system under discussion may well be comparable with that recorded by Greenwood and Werner. It may be noted that a similar relation obtains among the Group VI metals; in the system Sb—Sb₂S₃ there is a region of partial miscibility, whereas Bi and Bi₂S₃ are completely miscible, although the mixture is non-ideal. Further, published data show that increase in atomic weight of the metalloid also leads to increasing miscibility with metals, in the series telluride > selenide > sulphide > oxide. We may infer that increasing mutual polarisation between metal and metalloid—i.e., decreasing ionic character of the compounds—favours miscibility with metals.

Summary.

In the system Sn—SnS, there is a region of partial miscibility in the liquid state. The composition of the conjugate liquids has been determined from their melting point (858°) up to 1180° C. The eutectic in this system lies very close indeed to metallic tin.

¹² Friedrich and Leroux, *Metallurgie*, 1905, 2, 536.

¹³ Guertler and Moissner, *Metallk*, 1921, 18, 145.

ON CONDUCTIMETRIC TITRATIONS.

By RAYMOND S. AIRS AND MICHAEL P. BALFE.

Received 13th January, 1943.

PART I.—TITRATION OF ACIDS OF VARYING STRENGTHS IN ACETONE-WATER MIXTURES.

Known amounts of a number of typical acids, covering a range of dissociation constants, have been conductimetrically titrated, in acetone water mixtures of varying composition, with sodium hydroxide. These measurements were required to establish certain of the titration procedures described in Part II, but the titration curves, shown in the Figures, have some intrinsic interest.

The solvent mixtures were made up by volume. Most of the experiments were done with 0.05 milligram equivalents of acid in 25 c.c. of solvent, and to these the comments given below particularly apply. A number of experiments at different acid concentrations, also shown in the Figures, were made to establish the validity of the analytical method over a range of acid concentration.

In the cases of benzenesulphonic and hydrochloric acids, increased proportions of acetone in the solvent increase the conductivity of the salt. Possibly the increase in mobility by diminution in viscosity of the solvent more than counterbalances the effect of increasing interionic forces due to decreased dielectric constant. In the case of sulphuric acid the effect of solvent composition is obscured because at the neutral point in the higher concentrations of acetone the salt yields a monovalent anion and one cation, and in the lower concentrations of acetone, a bivalent anion and two cations. There is, however, evidence that at acetone concentrations above 80 % the effect with sulphuric acid is similar to that observed in the cases of benzenesulphonic and hydrochloric acids.

In some solutions, precipitation occurred after the end point was passed, being indicated by opalescence of the solution and by decreases in conductivity.

Fig. 1.—Titration of hydrochloric acid in acetone-water mixture.
 a. 0.05 mg. equiv. 90 % acetone.
 b. 0.05 " 85 % "
 c. 0.10 " 80 % "
 d. 0.05 " 80 % "
 e. 0.025 " 80 % "
 f. 0.05 " 70 % "
 (c. is plotted K - 220 and
 mg. equiv. - 0.05.)

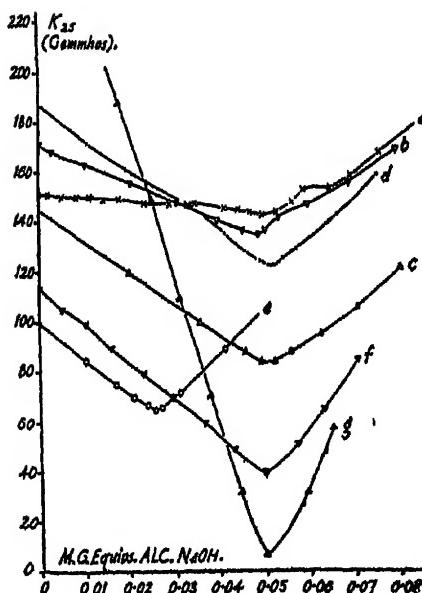
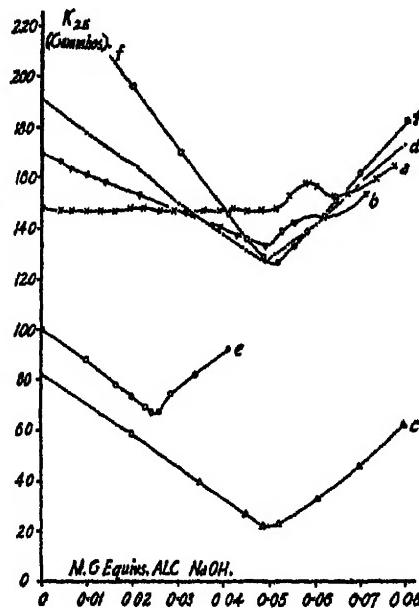


Fig. 2.—Titration of benzenesulphonic acid and picric acid in acetone-water mixture.
 a. 0.05 mg. equiv. } benzene- { 90 % acetone.
 b. 0.05 " sul- { 85 % "
 c. 0.10 " phonic- { 80 % "
 d. 0.05 " acid { 80 % "
 e. 0.025 " picric acid { 80 % "
 f. 0.05 " " { 80 % "
 g. 0.05 " " { 40 % "
 (c. is plotted K - 150 and mg. equivs. - 0.05,
 f. and g. are plotted K - 100.)

Hydrochloric acid (Fig. 1) is exactly neutralised at the point of minimum conductivity, in acetone of 85 % concentration or lower. In 90 % acetone, there is no fall in conductivity on converting the acid to its salt, but a rise occurs on addition of excess alkali, and is followed by precipitation.

Benzenesulphonic acid (Fig. 2) gives similar results to HCl, but even in 90 % acetone, there is a definite drop in conductivity on neutralisation, suggesting that in these conditions benzenesulphonic acid is a somewhat stronger acid than hydrochloric acid. Bolam and Hope¹ find that the conductivities of sulphonie acids indicate that they behave as strong acids in aqueous solution, toluenesulphonic acid being a simple strong acid, while there is evidence of micelle formation in the phenanthrenesulphonic acids.

Sulphuric acid (Fig. 4). -The end point is obscured by precipitation in 85 % and 90 % acetone. In 80 % acetone, the first dissociation is neutralised at the point of minimum conductivity, and in 40 % (and lower) acetone, both dissociations are neutralised. Between 80 % and 40 % acetone, the minimum conductivity moves progressively from the point corresponding to the first neutralisation to that corresponding to the second neutralisation.

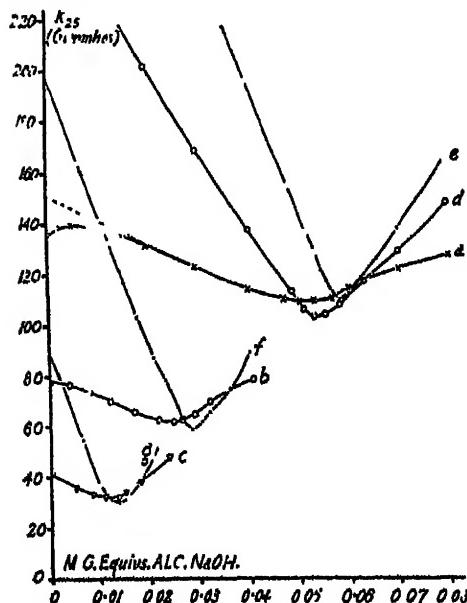


FIG. 3.—Titration of sulphurous acid in acetone-water mixture.

a. 0.10 mg. equiv.	80 %	acetone.
b. 0.05 "	80 %	"
c. 0.025 "	80 %	"
d. 0.10 "	60 %	"
e. 0.10 "	40 %	"
f. 0.05 "	40 %	"
g. 0.025 "	40 %	"

Picric acid (Fig. 2) is exactly neutralised at the point of minimum conductivity in 80 % and 40 % acetone. In 80 % acetone, the conductivity of sodium picrate (i.e. at the neutral point) is greater than that of sodium chloride (curve a, Fig. 1), though the mobilities (25°) of picrate and chloride ions, respectively, are given² as 30.0 and 76.3 in water and 84.5 and 105.1 in acetone. This may be due to variations in degree of dissociation of the salts in the different solvents (see Davies,³ pp. 228 *et seq.*).

Sulphurous acid (Fig. 3) behaves as a monobasic acid, neutralised at the point of minimum conductivity, in 80 % acetone, but even in 40 % acetone, very little of the second group is dissociated. This is probably due to combination with the acetone, giving a monobasic hydroxy-sulphonic acid, which may be the cause of an observed slow increase in conductivity to a steady value, after mixing the acid and solvent (conversion of sulphurous acid, $pK\ 1.77$, to a stronger acid). In 60 % and 40 % acetone, the titration was not started until equilibrium was reached. In 80 % acetone (0.1 mg. equiv.) the titration was started immediately after

¹ Bolam and Hope, J.C.S., 1941, 843.

² Davies, *Conductivity of Solutions*, 2nd Ed., London, 1933.

³ Landolt-Bornstein, *Tabellen*.

mixing the solution, and there is evidence that an increase in conductivity was occurring after making up the solution : (the extrapolated dotted line

FIG. 4.—Titration of sulphuric acid in acetone-water mixture.
 a. 0.05 mg. equiv. 90 % acetone.
 b. 0.05 " 85 % "
 c. 0.10 " 80 % "
 d. 0.075 " 80 % "
 e. 0.05 " 80 % "
 f. 0.025 " 80 % "
 g. 0.05 " 70 % "
 h. 0.05 " 60 % "
 i. 0.05 " 50 % "
 j. 0.10 " 40 % "
 k. 0.05 " 40 % "
 l. 0.025 " 40 % "
 m. 0.05 " 30 % "

(j. is plotted K = 210 and
 mg. equivs. = 0.05.)

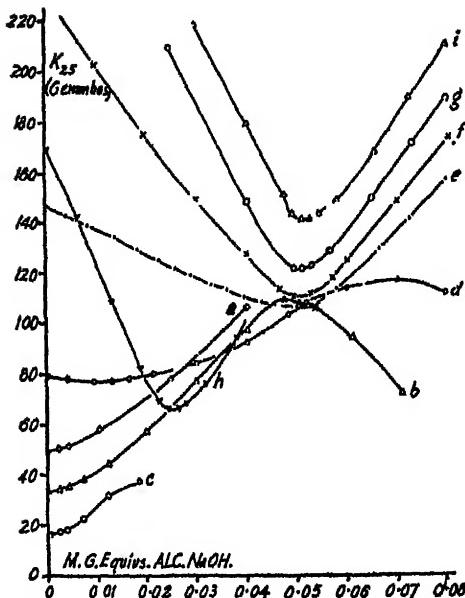
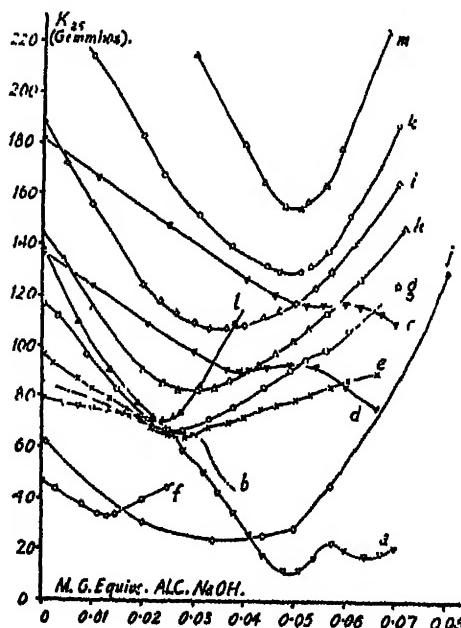


FIG. 5.—Titration of oxalic acid in acetone-water mixture.

a. 0.20 mg. equiv. 80 % acetone.
 b. 0.10 " 80 % "
 c. 0.025 " 80 % "
 d. 0.10 " 70 % "
 e. 0.10 " 60 % "
 f. 0.10 " 50 % "
 g. 0.10 " 40 % "
 h. 0.05 " 40 % "
 i. 0.10 " 30 % "

curve a, gives the suggested course of the titration if equilibrium had first been established).

Oxalic acid (Fig. 5).—The first dissociation is neutralised at the minimum conductivity, in acetone of 60 % concentration or lower.

Tartaric acid (Fig. 6) gives no minimum of conductivity on titration in 80 % acetone. From 60 % to 30 % acetone, the proportion of the acid titrated, at the minimum point, increases from 10 % to 50 % with 0.05 mg.

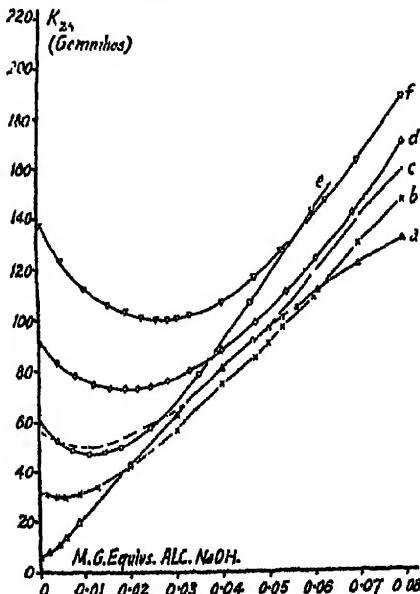


FIG. 6.—Titration of tartaric acid in acetone-water mixture.
 a. 0.10 mg. equiv. 80 % acetone.
 b. 0.10 " " 60 % "
 c. 0.10 " " 50 % "
 d. 0.10 " " 40 % "
 e. 0.05 " " 40 % "
 f. 0.10 " " 30 % "

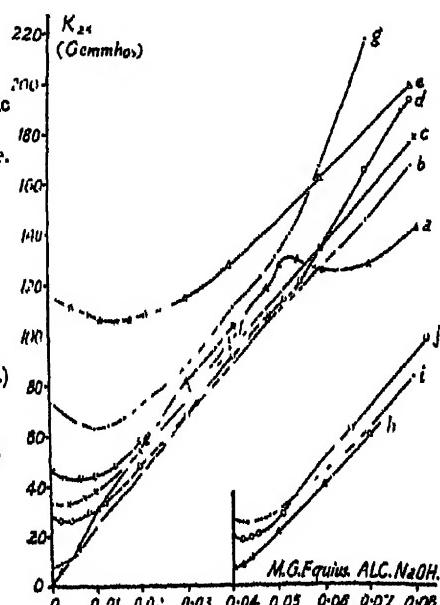
FIG. 7.—Titration of formic acid and acetic acid in acetone-water mixture.

a. 0.05 mg. equiv. formic acid	90 % acetone.	
b. 0.05 " " " 70 % " "	100	
c. 0.25 " " " 60 % " "	100	
d. 0.05 " " " 50 % " "	110	
e. 0.25 " " " 40 % " "	110	
f. 0.05 " " " 40 % " "	110	
g. 0.05 " " " 30 % " "	110	
h. 0.05 " " " 50 % " "	110	
i. 0.25 " " " 40 % " "	110	
j. 0.05 " " " 30 % " "	110	

(h., i., and j. are plotted mg. equivs. \times 0.04.)

Volume of solvent 25 c.c.

K_{25} = specific conductivity in gemmhos.
Alcoholic NaOH additions in mg. equivs.



equivs. of acid (first h) in 25 c.c. of solvent. In 25 c.c. of 40 % acetone, of 0.05 mg. equivs., 40 % were titrated at minimum conductivity, and of 0.025 mg. equivs., 50 %.

Formic acid (Fig. 7) appears to be completely unionised in 90 % acetone; in 70 %, a break in the titration curve at 0.06 c.c. may be due to a small

degree of ionisation. In 40 % acetone, less than 10 % of the acid present is titrated at the minimum conductivity.

Acetic acid (Fig. 7).—In 40 % acetone, less than 2 % of the acid is titrated at minimum conductivity.

With regard to the end points of the titrations, we conclude that acids of $pK < 2$ are exactly titrated at the minimum of conductivity, when the solvent contains 40 % or less of acetone, and acids of $pK < 1$ are exactly neutralised at the minimum point, if the solvent contains 80 % or less of acetone. In those solvent mixtures where the strength of the acid is not greatly diminished, extrapolation of the two branches of the titration curve (the customary procedure) gives satisfactory results, but when the ionisation of the acid is diminished by the acetone, this procedure is not applicable. Our empirical use of the minimum conductivity gives satisfactory end points within the limits which we set.

Experimental.

Measurements were made at $25^\circ \pm 0.02^\circ$. The bridge consisted of a Tinsley resistance box (10^{-1} to 10^6 ohms) and a Tinsley ratio arms box (10^3 ohms being used in each arm). Bridge input was from a valve oscillator with a telephone as detector. The bridge arms were arranged so that resistance box readings gave observed conductivities in gemmhos. The cell was of similar design to that illustrated by Davies⁴ (Fig. 24b, p. 239), fitted with a glass cap through which projected the tip of a 5 c.c. microburette (graduated in 0.02 c.c.). Cell constant 0.561, diameter 3 cm., height to shoulder 6 cm. Bright platinum electrodes and a bridge input of 3000 cycles were used. The water used, obtained from a Barra-glass still,⁴ had K_{ss} 1.2-1.5 gemmhos. Acetone was Analar grade.

PART II.—THE ANALYSIS OF COMPLEX MIXTURES OF ACIDS AND SALTS.

In connection with an investigation on tanning liquors, we have found it necessary to develop a method for examining dilute aqueous solutions which contain acids of all strengths, and their salts, in varying proportions. The method, which may be of use in other problems, determines total salt content, and divides the acids into three groups, of different strengths. A general feature of the method is that the results are based on titration figures, avoiding the use of theoretically drawn lines and intercepts, and of mobility values which cannot be checked by experiment. As Davies⁵ has pointed out, great caution must be used in the interpretation of results based on theoretical lines or assumed immobilities, in the examination of complex mixtures.

We do not ascribe a particularly high accuracy to the method, though it is capable of refinement. Its purpose is to attempt a classification of the acids and salts in mixtures too complex to be examined by other methods. It is therefore complementary to the methods described by Davies and Righellato⁶ (from which it is partly derived), since their methods were primarily devised, and are the more suitable, for determination of a single acid in the presence of a weaker acid.

1. Examination of Complex Mixtures.

Classification of the Acids Present.—The method depends in the first place on the use of a synthetic resin for removal of "bases" (i.e. substitution of hydrogen ions for other cations), as described by Brown,

⁴ Smith, *Chemistry and Industry*, 1938, 57, 963.

⁵ Davies, *J. Int. Soc. Leather Trades Chem.*, 1938, 22, 181.

⁶ Davies and Righellato, *Trans. Faraday Soc.*, 1933, 29, 429, 438.

Cheshire and Holmes.⁷ Having converted all the salts in the solution to acids, the resulting mixture of acids is divided into groups. Strong acids ($\rho K < 1$) are determined by titration in 80 % acetone. Strong acids and acids of medium strength ($\rho K < 2$) are determined by titration in 40 % acetone (see Part I). The total acid content, including all carboxylic acids but as far as possible excluding phenols is determined by a modification of the procedure introduced by Davies and Righellato,⁸ in which the end point is located at the intersection of titration curves with a strong and a weak alkali. The acids are then classified in three groups, which we describe as " $\rho K < 1$ acids," " $\rho K 1-2$ acids," and " $\rho K 2-7$ acids."

The use of aqueous acetone in the titration of strong acids is derived from Richardson's work.⁹ It gives better results than the procedure suggested by Davies and Righellato,⁸ in those cases where the amount of strong acid present is not sufficient to repress completely the ionisation of the carboxylic acids. With regard to the determination of total acid content, we found the procedures described⁸ for the potassium hydroxide-ammonia titration to be unsatisfactory with the solutions which we examine, since they contain, in addition to carboxylic acids of varying strengths, a variety of phenolic hydroxyl groups, and on account of partial interaction of the weaker base with these very weak acid groups, the plot of its titration does not show a horizontal portion, but rises continuously. Though the difficulty is less marked with sodium hydroxide-pyridine titration,¹⁰ the extensive hydrolysis of pyridine salts diminishes the precision of this procedure.

The equilibrium constant K_s for the interaction of an acid and a base, taking pyridine as the base, is given by

$$K_s = \frac{[C_6H_5NH^+][A']}{[C_6H_5N][HA]} = \frac{K_A}{K_B}$$

where K_A is the dissociation constant of the acid, and K_B is the association constant of the base; which in the case of

$$\text{pyridine} = 10^{-14}/2.3 \times 10^{-9} = 4.3 \times 10^{-6}$$

If the pyridine is present in large excess over the acid, then writing the initial concentration of acid as c , the concentration of pyridine as Pc and the fractional degree of salt formation as α ,

$$K_s = \frac{c^\alpha}{Pc^{1-\alpha}} = \frac{\alpha^2}{P(1-\alpha)} = \frac{K_A}{4.3 \times 10^{-6}}$$

From this relation, the extent to which an acid of known dissociation constant will be converted to salt, on addition of a known amount of pyridine, can be calculated. Table I compares calculated and experimental results, for a number of acids, in the case where the equivalent concentration of pyridine is a hundredfold that of the acid ($P = 100$).

Our method for titration of total acid content is based on the above principle, and on the similar mobilities of pyridinium and sodium ions. The conductivity of the solution of acids is determined after the addition of a large excess of pyridine. The end point is the point where the ascending portion of the sodium hydroxide titration curve passes through this conductivity value (a correction, described below, can be applied for the small difference in the mobilities of the two cations). We refer to this as the "pyridine end point." The use of pyridine in this way has the following advantages: a large excess of pyridine can be introduced without greatly

⁷ Brown, Cheshire and Holmes, *J. Inst. Soc. Leather Trades Chem.*, 1941, 25, 254; somewhat similar uses of base-exchange resins for analytical purposes have been described by Samuelson, *Z. anal. Chem.*, 1939, 116, 328; *Svensk. Kem. Tidskr.*, 1939, 51, 195; 1940, 52, 115, 241.

⁸ Richardson, *Proc. Roy. Soc. B*, 1934, 115, 170.

diluting the solution, by addition of 1 c.c. of the pure base; it reacts almost quantitatively with acids of pK 6 or lower; the extent of interaction with very weak acid (phenolic) groups is so low that comparatively large variations in the amounts of these groups present do not greatly alter the conductivity in the presence of excess pyridine; excess of pyridine which does not react with acid does not contribute significantly to the conductivity of the solution. A hundredfold excess of pyridine was used in the experiments described below, though other proportions may in some cases be more suitable. For example, addition of 1 c.c. of a 10% solution of pyridine (10-fold excess) would diminish the reaction with phenolic groups, without seriously diminishing the reaction with carboxylic acid, as can be shown by calculations for the case where $P = 10$ in the relation given above.

The above procedures rest on a somewhat arbitrary basis and the possibility of overlapping between the different groups cannot be excluded; it is impossible, by any type of titration, to separate acids whose dissociation constants differ by only one or two powers of 10. We are, however, able to record what proportion of acids of given dissociation constants will be returned in the different groups.

$pK < 1$ Acids.—Hydrochloric and benzenesulphonic acids, picric acid (pK 0.8) and the

first dissociation of TABLE I.—PERCENTAGE OF ACIDS OF VARYING DIS-SULPHURIC ACID ARE SOCIATION CONSTANTS WHICH ARE CONVERTED TO QUANTITATIVELY RE-SALT BY A HUNDREDFOLD EXCESS OF PYRIDINE.

recorded in this group. Sulphurous acid is quantitatively recorded as a monobasic acid in this group (see Part I).

pK 1-2 Acids.—In this group are quantitatively recorded, the first dissociation of oxalic acid (pK 1.4) and the second dissociation of sulphuric acid (pK 1.0). It may record up to 50% of acid of pK 3.0

Acid.	Dissociation Constant.	% Converted to Salt.	
		Calculated.	Observed.
Sulphuric (2nd H)	$1.2 \times 10^{-2}(1)$	100	100
Formic . .	$1.8 \times 10^{-4}(1)$	100	100
Acetic . .	$1.8 \times 10^{-5}(1)$	100	98
	10^{-6}	95	—
Maleic (2nd H)	$2.6 \times 10^{-7}(1)$	88	89
H ₂ S (1st H)	$9.1 \times 10^{-8}(10)$	67	71
	10^{-9}	34	—
	10^{-10}	12	—
Phenol . .	$10^{-10}(11)$	4	7
	10^{-11}	1	—

(e.g. first dissociation of tartaric acid), but since the proportion of such acid recorded in this group diminishes as the amount present increases, this lack of precision is to that extent less likely to cause serious confusion. This group may also include not more than 10% of formic acid (pK 3.7) (see Part I).

pK 2-7 Acids.—The limits of this group are indicated, on the one hand by the extent to which its stronger constituents are recorded in the pK 1-2 acids (see above) and on the other hand by the extent to which the weaker acids are included (see Table I). Since pK 2-7 is a somewhat wide range, we find it useful to make a rough measure of the strength of the acids in this group, which we describe as the "average pK "; as described below, this figure is also of use in a check on the accuracy of the analytical results. It is determined as the pH at the point at which the pK 2-7 acids are half-neutralised; the titration is done on a solution from which the "bases" have not been removed, and allowance is made for the presence of

⁹ Harned's results, quoted by MacInnes ¹⁴.

¹⁰ Chandler, *J. Amer. Chem. Soc.*, 1908, 30, 694.

¹¹ From International Critical Tables.

any pK_{2-7} acids in the form of salts in calculating the amount of alkali required to reach the point of half-neutralisation.¹²

Determination of Free Acid is made by the above "pyridine end-point" procedure on a solution from which the bases have not been removed.

Determination of Salt Content—Previously described conductimetric methods for determination of salt content do not give satisfactory results when applied to complex mixtures. Determination of salts of weak acids, by titration with standard hydrochloric acid⁴ depends on an assumed value for the mobility of the weak anion, and on complete representation of the ionisation of the liberated weak acid. Strong base-strong acid salts can only be determined by applying assumed mobilities to the intercept, on the conductivity axis, of the salt line in the titration of the weak acids with alkali, except in special cases, e.g., where precipitation methods can be applied.

A simple and delicate measure of salt content is, however, given by the difference in titrations of the solution before and after it has been passed through the base-removing resin. Brown, Cheshire and Holmes,⁷ from whom we derived this method, used potentiometric titrations, and we find it, in general, applicable to the conductimetric method. In considering whether it is applicable to any given type of solution, however, the following points should be considered : (i) It records salts of strong and weak bases, such as potassium salts and ammonium salts, but very weak bases, e.g. quinine, are partly displaced by pyridine at the first end point, and their salts thus partly recorded as free acid, with a corresponding decrease in the amount recorded as salt. (ii) If some acid molecules are co-ordinated with cations, they may be titrated at the first pyridine end point, but removed from solution, with the cations, by the resin. This will make the observed salt content too low. We have not investigated this point in detail, but in some of our analyses of tanning liquors, a break in the sodium hydroxide titration curve (before removal of bases) just before the pyridine end point is reached, coupled with other data, drew our attention to the possibility. (iii) It appears that from some solutions the resin may sorb small quantities of acid. We find this to occur, to a limited extent, in solutions which contain acid tannins; these are large molecules which contain carboxyl groups. We have not found any evidence of sorption of simple acids.

To guard against the above possibilities of error, we check the salt determination by an alternative method. The substance under examination, dissolved in 40 % acetone, is titrated with sodium hydroxide. At the point of minimum conductivity, only the free acids of $pK < 2$ are titrated. Since the total amount of these acids present is known, the amount present as salts can be calculated, and is the total salt content of the substance. If, on the other hand, all the $pK < 2$ acids are in the form of salts, and possibly some of the pK_{2-7} acids also, a known amount of HCl is added to the solution in 40 % acetone, to displace pK_{2-7} acids from their salts. The titration then gives the residual free HCl, and the difference between this and the amount of HCl added is equivalent to the salts of pK_{2-7} acids. This quantity, added to the content of $pK < 2$ acids, which in the first approximation must in this case all be present as salts, gives the total salt content of the substance.

This method is less delicate than the "two pyridine end-points" method, because it involves the sum of several separate operations, and because the conductivity changes in the above titration are small. It is in the first place useful as a check on the pyridine end-points method, but might be used alone in cases where the latter is vitiated.

¹² The useful procedure described by Philpot, Rhodes and Davies (*J.C.S.*, 1940, 84), for calculating the approximate dissociation constant of an acid from its conductimetric titration, is not applicable to mixtures of acids.

Check on the Results.—As the method is somewhat arbitrary, we check the conclusions by an independent measurement, by calculating, from the pH value of the solution, the proportion of the different types of acids which are present as salts, and comparing the sum of these calculated salt contents, with the observed salt content of the solution. A useful expression for the proportion of any acid present as salt is given by Mysels;¹³

$$b = \frac{1}{1 + 10^{\delta K} \rho H}, \text{ where } b \text{ is the proportion of acid in the form of salt,}$$

δK and ρH refer to acid and solution respectively.

2. Experimental Methods.

General discussions of the methods of conductimetric titrations are already available,^{2, 7, 14} and we only describe here the special features of our application. The apparatus for titrations in acetone solutions is described in Part I. Analar or recovered acetones were used; the water content of the latter was checked by determining its conductivity after saturation with KCl (the value increases rapidly with water content). Analar acetone saturated with KCl had K_{ss} 5 gemmhos. A mixture of 99 c.c. Analar acetone and 1 c.c. conductivity water, saturated with KCl had K_{ss} 17 gemmhos, and we rejected any recovered acetone which came above this limit.

For titrations in aqueous solution, the same bridge was used. The cell (diameter 6 cm., height to shoulder 12 cm., cell constant 0.118, the side arms for electrode connections being mainly outside the body of the cell) was similar in shape to that used in the acetone titrations, and fitted with an inlet tube for CO_2 -free air, or inert gas, entering half-way down the body of the cell. The working capacity of the cell, approximately 220 c.c., brought the solution level up to the inlet tube.

Since we worked with very dilute solutions, we found the use of bright platinum electrodes necessary to avoid adsorption errors. The catalytic action of platinum black has also to be considered when dealing with solutions of unknown composition; for example, it causes difficulty in titrating solutions which contain formic acid. To diminish polarisation, a bridge input of 3000 cycles was used (on occasion, a balancing capacity parallel to the resistance box was helpful).

Mobility of Pyridinium Ion.—The horizontal portion of the titration curve of 0.566 mg. equivs. of HCl with 0.05 N pyridine in 250 c.c. water, corresponded to K_{ss} 275 gemmhos. A 0.00453 molar solution of pyridinium chloride, in the presence of excess of pyridine, had K_{ss} 539 gemmhos. Using Robinson and Davies'¹⁵ correction for interionic forces, and taking 76.3 (from MacInnes¹⁶) as the mobility of chloride ion, these two results give 47.6 and 48.4, respectively, for the mobility of pyridinium ion at 25°. The average, 48.0, is sufficiently accurate for our purpose. For the sodium ion, MacInnes¹⁶ quotes a mobility of 50.1.

Base-removing Resin.—The preparation and use of the resin has been described by Cheshire, Brown and Holmes'; a base-exchange material of this type can be obtained from the Permutit Co., Ltd., under the designation "Zeo-Karb H.I."

Solutions under test are percolated through about 15 g. portions of the resin (in tubes of about 1 inch diameter). Immediately before each use the resin is washed with 200 c.c. of distilled water percolated in 1 hour, followed by 70 c.c. conductivity water percolated in 20 minutes. Portions of the test solution, containing about 0.1 mg. equivs. of salt, dissolved in 90 c.c. conductivity water, are run through the resin in 20 minutes, followed

¹³ Mysels, *J. Chem. Educ.*, 1941, 18, 478.

¹⁴ Britton, *Conductometric Analysis*, London, 1934.

¹⁵ Robinson and Davies, *J.C.S.*, 1937, 574.

¹⁶ MacInnes, *Principles of Electrochemistry*, New York, 1939.

by 90 c.c. wash water in 20 minutes, the percolate and washings being mixed. Used in this way we find that 10 g. of resin remove the base from 5 mg. equivs. of KCl with an efficiency of 99.5% (the efficiency then falls, being 60% when 10 mg. equivs. of KCl have been treated). We regenerate the resin when 2.5 mg. equivs. of salt have passed through it.

The resin is regenerated by contact with 2 N HCl for 1 hour, then washed with 1500 c.c. distilled water, in the course of which it should stand overnight in contact with the water. Immediately before use, the resin is washed with conductivity water (90 c.c., 45 minutes percolation). At any stage of its history the resin tends to yield acid to the wash water; if the final washing water has $K_{25} > 6$ gemmhos, we repeat the washing. A correction may be made for the amount of acid taken up by the test solution during percolation through the resin; this is of the order of 0.1 c.c. of 0.02 N per 200 c.c. of percolate.

Titration of Acids in Acetone Solution.--The combined solution and washings, after percolation through the resin, are evaporated below the boiling-point to a small volume (5-10 c.c.) and transferred to the cell, with the appropriate amounts of water and acetone to give total volumes of 25 c.c. of 80% or 40% acetone, according to the group of acids being titrated. The solution is titrated with 0.1 N alcoholic NaOH, and observed conductivities are corrected to 25 c.c. for plotting. The end point is at the minimum conductivity, but the total titration should not exceed 0.5 c.c., since if the amount of acid being titrated is high, its ionisation may have been repressed to an extent which will prevent the end point of titration from coinciding with the minimum conductivity and errors due to precipitation may also arise.

Titrations in Aqueous Solution.--The following procedure is used for solutions before and after passing through the resin, the titration being made with 0.05 N aqueous NaOH in a volume of approximately 220 c.c. Observed conductivities are corrected to 220 c.c. for plotting. A current of CO₂-free air (or other suitable gas) is passed through the cell, over the surface of the liquid, for 30 minutes before adding any alkali, with occasional vigorous shaking. Though the CO₂ in the water we used is not of great importance (the amount of CO₂ required to give $K_{25} 1.2$ gemmhos in water would give $K_{25} 1.7$ gemmhos when converted to pyridinium or NaIC(O₂), yet it is desirable to exclude the CO₂ of the outside air, particularly in the case of the pyridine titration, where uptake of CO₂ by the large excess of base would cause a gradual increase in the conductivity. (Table I shows that there will be appreciable interaction between carbonic acid, $K_{25} 4.5 \times 10^{-7}$ ⁽¹⁸⁾ and pyridine.)

Pyridine.--One c.c. of Analar pyridine is added to the solution with shaking and the conductivity then recorded.

Sodium hydroxide.--The alkali can be added in fairly large (0.5 c.c.) amounts until the ascending portion of the curve is approaching the conductivity of the pyridine salt; additions are then made in 0.02 c.c. portions. Our limits (e.g. as shown in Table I) have been worked out for conditions where the total titration is less than 5 c.c.

The correction for the difference in mobility of the two cations is

$$\frac{(A_{Na} - A_{pyridine}) \times 10^8}{1000} \times \frac{N}{V \times C} \times 7$$

where N = normality of the NaOH.

V = volume of solution in the cell.

C = coll. constant.

T = c.c. of NaOH added at end point.

It can be reduced in the present case, with sufficient accuracy, to the following procedure. The volume (c.c.) of 0.05 N NaOH added at a point where the conductivity in the NaOH titration is approximately equal to the pyridine salt conductivity, is multiplied by four and the product is

added to the pyridine salt conductivity (in gemmhos). The result is the conductivity of an amount of sodium salt equivalent to the amount of pyridine salt formed, and the end point is the point at which the sodium hydroxide titration passes through this conductivity value.

The experimental results given in Table I were determined by the above method, 0·1 mg. equivs. of the acids in question being taken for titration in the form of suitable volumes of solutions of known strength (0·2 mg. equivs. of sulphuric and maleic acids were used and allowance was made for titration of their first dissociation). The phenol solution was made up by weight, the strengths of the other solutions were determined by titration, iodimetrically in the case of the Li₂S solution, and with 0·05 N NaOH, using a suitable indicator, in the other cases.

"Average pK."—Fifty c.c. of solution, containing of the order of 5 mg. equivs. of acid, are titrated with 0·2 N NaOH, pH being measured with the Cambridge Instrument Co.'s "pH Meter" and glass electrode.

Salt Determinations.—The following results by the pyridine end-point method indicate the scope of the method. From 0·01 mol. of KCl, in 90 c.c. of water, 96 % of the theoretical amount of acid was found after passing through the resin; other results with KCl are given above. From 0·053 millimol. of quinine hydrochloride, 90 % of the theoretical amount of acid was found. From 0·1 mg. equivs. of H₂SO₄, half-neutralised with NaOH, and from 0·1 mg. equivs. of acetic acid, similarly half-neutralised, the recovery of acid was quantitative.

The pyridine end point in the titration of a solution containing 0·004 mg. equivs. of acetic acid and 0·020 mg. equivs. of ammonium hydroxide corresponded to the titration of 0·074 mg. equivs. of acid. The pyridine end point in the titration of 0·053 millimol. of quinine hydrochloride corresponded to the presence of 0·014 mg. equivs. of free acid. Thus ammonia is not displaced at the pyridine end point, but some 25 % of the very weak base, quinine, is displaced.

With regard to the possibility that acid may be absorbed by the resin, a tannin solution was passed through the resin at the prescribed dilution, and reconcentrated. It then contained 79 mg. equivs. of acid per litre. A portion of this concentrated solution after passage through resin which had been freshly regenerated and washed (*i.e.* should not contain cations which might remove acid by co-ordination) was found to contain 72 mg. equivs. of acid per litre.

The principle of the acetone titration for determination of salts is described above. To a portion of the test solution, with addition of 5 c.c. of 0·002 N HCl if there are no free $pK < 2$ acids present, water and acetone are added in amounts to make a total volume of 25 c.c. of 40 % acetone. The solution is titrated with 0·1 N alcoholic NaOH. The titration should not exceed 0·05 c.c.

The following experiments illustrate the method. Titration of a solution containing 0·100 millimol. of sodium acetate and 0·150 mg. equivs. of HCl showed that it contained 0·055 mg. equivs. of free acid. A solution of 0·050 mg. equivs. of HCl and 0·020 mg. equivs. of ammonia was found to contain 0·030 mg. equivs. of free acid. In titrating quinine hydrochloride, the curve rises from the start, *i.e.* quinine is not displaced. Pyridine is almost entirely displaced; titration of 0·050 mg. equivs. of HCl and 0·020 mg. equivs. of pyridine showed the presence of 0·049 mg. equivs. of free acid.

3. Examples.

The results in Table II (in mg. equivs. per litre) were obtained on analysis of two tanning liquors.

Liquor A is an example of the more common type of results where the acetone-HCl salt determination supports the pyridine end-points method, and we therefore use the latter figure.

The amounts of the different acids present as salts are : $pK < 1$, 1.5 ; $pK 1-2$ (using $pK 2$ for calculation), 13.0 ; $pK 2-7$, 31.8. The sum of these, 46.3 mg. equivs. per litre, is in fair agreement with the observed figure, 44.0.

Liquor B. This is an example of the less common type of results, in

	A	B
$pK < 1$ acids	1.5	3.0
$pK 1-2$ acids	13.0	0.5
$pK 2-7$ acids	53.8	71.8
Free acid	24.2	60.8
Salts { by pyridine end points	44.0	3.0
by acetone-HCl titration	42.5	14.5
Average pK of " $pK 2-7$ acids "	4.2	4.7
pH	4.36	3.24

which the pyridine end points give too low a salt content, but the acetone-HCl method gives a satisfactory result, and we take 14.5 mg. equivs. per litre as the salt content of the solution. Since in such cases we have evidence that acid is removed from tanning liquors on passing through the resin, we add the difference between the two salt

contents to the second pyridine end point before calculating the total acid content (from which the amount of the $pK 2-7$ acids is derived).

The calculated salt contents are : $pK < 1$, 3.0 ; $pK 1-2$, 0.0 ; $pK 2-7$, 2.5 ; total 14.5, thus justifying the use of the acetone-HCl results.

Summary.

Part I.—Describes conductimetric titrations of acids of varying dissociation constants, in acetone-water mixtures of varying compositions, with 0.1 N alcoholic sodium hydroxide.

Part II.—Describes a procedure for the examination of complex mixtures of acids and salts by conductimetric titrations. For the classification of the acids, the bases are first removed by a synthetic organolith, and the acids then separated into groups by titrations, (A) in 80 % acetone, (B) in 40 % acetone, (C) in water. Strong acids ($pK < 1$) are recorded in (A) ; acids of $pK 1-2$ are equivalent to B-A ; acids of $pK 2-7$ are equivalent to C-B. Salt content is determined by the difference between titrations of the solution before and after the bases have been removed ; an alternative method is also described.

The procedure for determining the end point, in the titration of total acidity, is devised to record all carboxylic acids, and to exclude, as far as possible, phenolic groups.

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LATENT IMAGE FORMATION.*

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I. Nature of the Photographic Latent Image.

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Since the publication in 1938 of the paper by Gurney and Mott¹ on the photolysis of silver bromide and the photographic latent image, a considerable volume of research has accumulated which was largely stimulated by that paper. The basic conceptions of Gurney and Mott still stand, but many of the smaller details have to be recast in the light of more recent experiments. It is the purpose of this paper to present the revised theory in as coherent a form as possible, considerations of space precluding any attempts to go into great detail in those cases where alternative explanations have been put forward. A few recent unpublished

* Communication No. H. 884 from the Kodak Research Laboratories.

¹ Gurney and Mott, *Proc. Roy. Soc. A*, 1938, 164, 151.

experimental results have been included. In several cases tentative suggestions have been made where there appeared to be gaps in either the theory or the experimental data.

I. Nature of the Photographic Latent Image.

The photographic latent image has for a long time been regarded as a minute speck of metallic silver,² which serves as a catalyst enabling the developing solution to distinguish between exposed and unexposed grains. We shall here adopt that assumption and try to account for the formation of the latent image on the basis of the known physical properties of the silver halide, making up the photographic grains. We can hardly do better, since the amount of latent image formed by ordinary exposures is so minute that the experimental evidence on its nature is necessarily indirect. The processes occurring when light is absorbed by silver halides can, however, be conveniently studied on single crystals, although the two cases are not strictly analogous. In photographic emulsion grains, the ratio of surface area to volume is relatively large compared with the single crystals, and impurities play a correspondingly large part in emulsion grains. It is profitable, however, to understand the mechanism of light absorption and of the electrical properties of pure silver halides in order to extrapolate to the case of impure materials.

II. Single Crystals and Emulsions.

(a) Absorption of Light.

The light absorption of silver halides differs from that of most of the other ionic crystals in one very important respect. Instead of the sharply defined bands found, e.g. with the alkali halides, spectral absorption falls but slowly, and can be measured a long way, towards longer wavelengths.³ This has been accounted for by the assumption that the surface ions are considerably more loosely bound than those in the body of the crystal.⁴ A large single "real" crystal has been regarded as being built up like a house of bricks of a large number of very small "ideal" mosaic crystals;⁵ the more loosely bound ions occur on all the interfaces between the individual ideal crystals and so form an appreciable fraction of the total number of ions available.

The existence of this long absorption tail is of crucial importance for the formation of the latent image. If one imagines an emulsion made up from one of the alkali halides which have a well-defined absorption band, one can see at once that all the light which the grains are capable of absorbing will be absorbed in the first layer apart from a very small range of wavelengths. With silver halides, a far wider range of wavelengths is capable of penetrating into the depths of a photographic emulsion and of registering itself as a latent image.

The assumption that the surface ions are loosely bound is further supported by the fact that their absorption (or at least the absorption tail) is easily changed by impurities. It is to be assumed that adsorbed impurities, by electric or other interference, change the binding energy of the surface ions, and thus their absorption spectrum. Thus the long wavelength absorption of silver halide differs considerably for different specimens and is therefore not entirely characteristic for the material.

² See, for instance, Abegg, *Wied. Ann.*, 1801, 62, 425; Ostwald, *Lehrb. allg. Chemie*, Leipzig, W. Engelmann, 1893, Vol. 2, Part 1.

³ Fizefeldt and Gyulai, *Nachr. Ges. Wiss. Göttingen, Math. Phys. Kl.*, II, 1929, 226.

⁴ Herzfeld, *Z. physik. Chemie*, 1923, 105, 340.

⁵ See Ott, in Wien and Harms' *Hab. Experimentalphysik*, VII, Part 2, Leipzig, 1928, p. 101 *et seq.*

(b) Electronic Processes.

(1) Photo-conductivity.—A silver halide crystal kept in the dark at low temperature is an insulator. Illumination by light of a wavelength absorbed by the crystal in the absorption tail mentioned in the previous section produces a conductivity of electronic nature.⁶ For every quantum of light absorbed, an electron can be drawn across the crystal to the anode, if the electric field strength is sufficient.⁷ It is important to note, however, that some of these electrons are trapped if the field strength is too small; the nature of these traps is unknown.⁸

The electrons carrying the photo-current are considered to be removed from the bromine ions in the lattice and raised (in energy) into the so-called conduction levels of the crystal.^{1, 8} The electron moves about in the conduction levels with thermal energy, its velocity being of the order of 10^7 cm./sec. Its diffusion coefficient is of the order of 1 cm.²/sec.

A crystal of silver halide containing small amounts of colloidal metallic particles such as occur in latent image formation shows the effect of trapping of electrons to a much greater degree than a pure crystal.⁹ This

SILVER HALIDE
CONDUCTION LEVELS.

Ag METAL
OR Ag₂S

FIG. 1.—Electron levels in silver halide and silver or silver sulphide.

means¹ that the conduction levels of silver are below those of the silver halides, so that electrons passing from the silver halide into a silver speck cannot easily return (Fig. 1).

(2) Bromine Atoms.—Absorption of a quantum of light thus leaves us with a mobile electron, and a halogen atom somewhere in the lattice at the place where the act of absorption occurred. The fate of this atom is not clear. There is evidence that at least some of the halogen leaves the crystal and is taken up by the surrounding gelatine in a photographic emulsion. This is easily understood if it is assumed that most of the absorption of light occurs near the surface of the silver halide grain. That assumption is fairly legitimate, since the size of the mosaic crystals in silver halides is of the order of the grain size of photographic emulsions.¹⁰ (See also Section V c 3.) We can thus picture our photographic grain as a nearly perfect crystal in which only the surface ions are sufficiently loosely bound to cause absorption at long wavelengths.

Halogen atoms appear to be fairly mobile even inside a silver halide crystal: colloidal silver formed inside a single crystal of silver bromide, presumably along internal cracks, can be re-formed into silver bromide by treating the crystal with bromine, water and other oxidizers.¹¹ The mobility is probably not a mass transport, but an electronic process of replacement; a halogen atom moves to a neighbouring place occupied by a halogen ion

⁶ See Tubandt, in Wied and Harms *Hdb. Experimentalphysik*, XII, Part 1, Leipzig, 1932; Wilson, *Ann. Physik*, 1907, 22, 107.

⁷ Lehnfeldt, *Nachr. Ges. Wiss., Göttingen, Math. Phys. Kl.*, II, 1935, 170.

⁸ Wilson, *Proc. Roy. Soc. A*, 1931, 133, 458; *ibid.*, 1931, 134, 277; *ibid.*, 1932, 136, 487.

⁹ Pohl, *Proc. Physic. Soc.*, 1937, 49 (extra number), I.

¹⁰ Unpublished experiments by Dr. G. W. W. Stevens, see also *Phot. J.*, 1942, 82, 42.

by an electron jumping from the ion to the atom. Because of the wave-mechanical "tunnel effect" no activation energy is required for this process; a halogen atom may thus be as mobile as an electron in the conduction levels. The halogen atom may be trapped, however, by polarizing the surrounding lattice and thus "digging its own hole" in the way described by Mott.¹¹ For this process to occur, the atom has to remain stationary for about 10^{-8} seconds. It is clear that this high mobility of bromine atoms would make latent image formation impossible (see Section IIIa), unless the bromine is removed from the grain.

This consideration, however, is not conclusive. The reason is that even if an electric field attracts a bromine atom, the movement of the atom towards the source of that field is a diffusion process. Thus, if a bromine atom were formed inside the lattice, there is a very high chance of the atom touching the surface of the crystal when it would combine with the surrounding gelatine, before it could attack the growing latent image speck. From this point of view then, we would have to say that the longer wavelengths of light are certainly absorbed by more loosely bound ions, but that these ions may equally well be situated on internal cracks and imperfections as on the true geometrical surfaces of the crystal.

(3) Electrons from Colloidal Silver. The colloidal silver formed in silver halides by the small exposure to light necessary to form a latent image is itself capable of absorbing light and was, in fact, discovered by the discoloration so produced in the crystals.¹² The absorption of light separates an electron from the speck of silver so as to become a free electron in the silver halide lattice: it is lifted in energy from the levels in the speck into the conduction levels of silver halide. The limiting wavelength of this internal photo-electric effect would, if it were well defined, give the energy difference between these levels. Since this is not the case, it has been concluded that the electron levels in a colloidal speck of silver are lower, the larger the speck, which is only another way of saying that a larger speck is more stable than a smaller one.¹³ A very small speck might lose electrons into the conduction levels of silver halide by thermal agitation energy, and if the electrons so lost are trapped somewhere else and do not return, the speck would disintegrate by an ionic process to be discussed below. If single crystals are illuminated by monochromatic light in the silver absorption band, absorption in that part of the band which is near to the wavelength used ceases, while that in the parts of the band further away from that wavelength continues. This is further justification for assuming that the particles causing the absorption band are not homogeneous and, in fact, of colloidal nature and of varying size.¹⁴

(4) Herschel Effect. A similar effect occurs in photographic emulsions in which, under suitable conditions, illumination with red light causes a bleaching of a latent image produced, say, by blue light. This effect is now known as Herschel effect (although the effect originally described by Herschel refers to the print-out, not the latent image). The wavelength distribution of the Herschel effect corresponds quite closely to the silver absorption band in silver halide crystals,¹⁵ and supports the view that the particles causing the absorption in single crystals are identical with the photographic latent image.

(c) Ionic Processes.

At normal temperatures, silver halides exhibit electric conductivity, even in the dark.¹⁶ The carriers of a current passing through a crystal

¹¹ Mott, *Proc. Physic. Soc.*, 1938, 50, 186.

¹² Hilsch and Pohl, *Z. Physik*, 1930, 64, 606.

¹³ Löhle, *Nachr. Ges. Wiss. Göttingen, Math. Phys. Kl.*, 11, 1933, p. 271; see also de Boer, *Electron Emission and Absorption Phenomena*, Cambridge, 1935, p. 299.

¹⁴ Carroll and Kretchman, *Bur. Stand. J. Res.*, 1933, 10, 449; Bartelt and Klug, *Z. Physik*, 1934, 89, 779.

under these conditions are silver ions, moving by means of two different mechanisms (as illustrated in Fig. 2).

(1) Interstitial Ions.—In thermal equilibrium some of the silver ions can be shown to occupy interstitial positions in the centre of the unit cube of the structure.¹⁵ In these positions they are mobile, although requiring a certain activation energy (8200 cal./mol. for AgBr, 6500 cal./mol. for AgCl). The energy of formation of interstitial silver ions is 20,200 cal./mol. for AgBr, and 25,000 cal./mol. for AgCl. Their concentration is given by a formula of the type $C = C_0 e^{-W/kT}$, and is of the order of 10^{-6} for AgBr and 10^{-8} for AgCl at room temperature.¹⁶

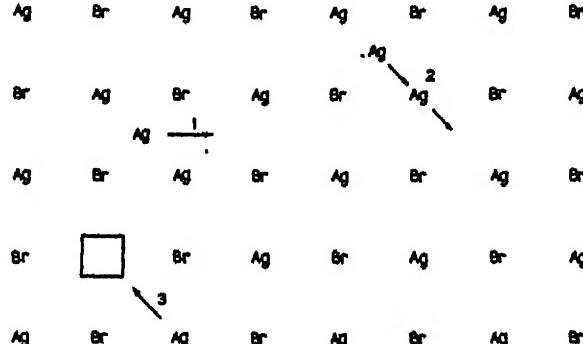
It is of interest to see how quickly the concentration of interstitial ions is formed at room temperature, assuming that we start from a crystal containing no interstitial ions at all. The probability that a certain ion goes into an interstitial position during time dt is

$$p' = A e^{-W/kT} dt,$$

and that a fraction C out of a total of N ions goes into these positions is

$$p = N C p' = N C A e^{-W/kT} dt.$$

FIG. 2.—Movement of silver ions in a silver bromide crystal. In mechanism 1 and 2, ions move into new interstitial positions; in 3 an ion moves from a normal position into a hole \square , i.e. into another normal position.



The data above enable this equation to be evaluated, the only unknown factor being A , which is of the order of the molecular vibrations in the crystal and, according to Mott,¹⁷ between 10^{16} and 10^{18} , the lower value being more likely.

Evaluation gives for $T = 293^\circ$ K. AgBr : $dt \propto 10^{-8}$ to 10^{-6} seconds, according to whether the lower or the higher value of A is used, and similarly AgCl : $dt \propto 2 \times 10^{-8}$ to 2×10^{-1} seconds.

(2) Holes.—The hole left in the structure by the movement of an ion to an interstitial position also has a certain mobility, the mechanism here being a replacement: a neighbouring ion jumps into the hole, leaving a hole at the place whence it came.¹⁸ The activation energy for this process is of the same order of magnitude as that of the movement of the interstitial ions. The holes and interstitial ions thus contribute nearly the same amount to the electrolytic conductivity.

The concentration of interstitial ions in a particular crystal may be influenced by two factors. The presence of impurities might produce surplus interstitial ions or holes, the concentration of which would not depend on temperature. Secondly, the crystal might not be in thermal equilibrium. That means that a crystal at low temperature may contain

¹⁵ Jost, *Trans. Faraday Soc.*, 1938, 34, 860; Koch and Wagner, *Z. physik. Chemie B*, 1937, 38, 295.

¹⁶ Berg, *Proc. Roy. Soc. A*, 1940, 174, 559.

¹⁷ Mott, private communication; see also ref.¹.

a concentration of interstitial silver ions or holes corresponding to equilibrium at a higher temperature.^{7, 10, 16}

III. Latent Image Formation.

(a) Mechanism.

We have seen that absorption of light in a silver halide crystal liberates photo-electrons at various places all over the crystal, and that the crystal always contains mobile silver ions. How can these facts be used to account for the finding that metallic silver is eventually formed at one or two specks on or in the crystal?

It has been demonstrated that photographic emulsions are very insensitive to light, unless certain impurities were present during the manufacture of the emulsion. It was suggested¹⁸ that these impurities serve as nucleating centres for the latent image silver; the centres were found to be chemically well defined and to consist as a rule of silver sulphide.¹⁹ Gurney and Mott¹ have assumed that these "sensitivity specks" act by trapping the photo-electrons. They will thus become negatively charged and attract the mobile interstitial silver ions, which become discharged on the speck. In this way, a speck of metallic silver attaches itself to the silver sulphide speck.

The basic assumption, then, is that the electron levels in the silver sulphide speck are lower than the conduction levels of silver halide, so that an electron, on hitting the speck, can reach a state of lower energy (Fig. 1). This suggestion has not so far been confirmed experimentally. It is likely, and has, in fact, been demonstrated,¹⁸ that silver sulphide is not the only impurity which is effective as an electron trap. Probably all sorts of mechanical imperfections, as well as other chemical impurities, can act as traps. This would seem to be clear from the fact that latent image silver can also be formed in the interior of the photographic grains²⁰ where a normal developer does not reach and where sensitivity specks do not, as a rule, appear to exist (see Section IIIc).

(b) Size of Latent Image.

It is commonly assumed that a silver speck has to be above a certain size in order to induce development. The size of a latent image speck has, however, never been determined directly. All the calculations on the amount of silver required to make a grain developable were made on a statistical basis, assuming a certain quantum equivalence. For direct photolysis, i.e. for printing-out, a quantum efficiency of the order of 1·0 has been found.²¹ Certain upper and lower limits can be obtained in this way. Other calculations are based on the shape of the toe of the characteristic curve²² containing, in many cases, tacit and unwarranted assumptions on the mechanism of latent image formation and growth. Sheppard²³ has given a comprehensive review of the question, and concludes that in certain cases at the threshold one quantum, quite often a few, and on the average (density of 1) a few hundred, and sometimes several thousand quanta have

¹⁸ Svedberg, *Phot. J.*, 1922, 62, 310; Sheppard, *Colloid Symposium Monograph*, New York, 1923, p. 346.

¹⁹ Sheppard, *Phot. J.*, 1925, 65, 380.

²⁰ (a) Lippmann-Cramer, *Kolloidchemie und Photographie*, 2nd ed., Steinkopff, Dresden, 1921; (b) Kempf, *Z. wiss. Phot.*, 1937, p. 235; (c) Berg, Marringo, Stevens, *Phot. J.*, 1941, 81, 413.

²¹ Eggert and Noddack, *Z. Physik*, 1923, 20, 299.

²² Svedberg, *Z. wiss. Phot.*, 1920, 20, 36; Svedberg and Anderson, *Phot. J.*, 1921, 61, 325; Silberstein and Trivelli, *J. Opt. Soc. Amer.*, 1938, 28, 441; Silberstein, *ibid.*, 1941, 31, 343; Webb, *ibid.*, 1941, 31, 559; Brentano and Baxter, *Trans. Faraday Soc.*, 1940, 36, 581.

²³ Sheppard, *Phot. J.*, 1931, 71, 331.

to be absorbed by a grain. In these latter cases there is no need to assume that all the silver aggregates in one speck.²³ As an example, see the discussion on several competing sensitivity specks below. Any latent image theory has, however, to account for the fact that grains can be made developable on formation of quite a few silver atoms. In contradiction to this conclusion Savostjanova²⁴ claims that it is possible to "see" the colloidal silver particles produced by light in silver halide crystals under the ultra-microscope. She works out their diameter to be of the order of 1000 Å. It has been suggested, however,²⁵ that the particles are visible by a fluorescence process: some of the electrons released when light is absorbed by the system silver-silver halide drop back into the silver under the emission of light. This suggestion has not so far been investigated experimentally.

(c) Size of Sensitivity Speck.

In order to understand the mechanism of formation of the silver sulphide sensitivity specks, it is necessary to give a brief and very much simplified description of emulsion making.²⁶ This takes place in two principal stages. In the precipitation and ripening stage, alkali halide and silver nitrate solutions are mixed, and the nearly insoluble silver halide is precipitated. On continued heating in the solution containing surplus halide ions acting as a silver halide solvent, the larger crystals grow at the expense of the smaller ones, a process known as Ostwald ripening. In this stage, certain organic compounds normally present in the gelatine and containing labile sulphur molecules form adsorption complexes with the silver halide.²⁷ At the end of this process, we are left with a range of grains of varying size, having attached to their surfaces randomly distributed molecules of the adsorption complex. We have no compelling reason to assume that these molecules are distributed in any other way, although the formation of sensitiser molecules is sometimes regarded as an autocatalytic reaction.²⁸ After washing and consequent removal of any surplus halide ions, the emulsion is usually subjected to the second stage of heat treatment, known as digestion. Here, because the solvent halide ions are now absent, no more grain growth takes place, but the adsorption complexes already present, and any others which might be formed during digestion, are now reduced to silver sulphide, the more completely the longer the heat treatment. The random distribution of adsorption complexes leads to a random distribution of silver sulphide molecules, in which the chance of getting aggregates of a certain size follows a modified Poisson distribution. A relatively large total of adsorbed molecules is required to ensure that one chance aggregate of only a few silver sulphide molecules be formed per grain. From figures by Sheppard²⁹ on the amount of sensitiser necessary to produce optimum sensitisation, the size of a sensitivity speck is then of the order of 10 molecules.²⁸ It is likely that Sheppard's figures are on the high side, since they may include complex molecules not yet reduced to silver sulphide. The figure of 10 molecules may thus be regarded as an upper limit.

As digestion time is increased beyond the optimum two effects are observed.²⁸ First, the sensitivity of the emulsion drops. This may be due to the formation of more than one of the optimum size specks on some of the grains; competition between these reduces the sensitivity.²⁸ Secondly, the log value rises, i.e. there is an increasing number of grains,

²⁴ Savostjanova, 9^e Congrès International de Photographie, Paris, 1935, p. 94.

²⁵ Borg, *Trans. Faraday Soc.*, 1938, 34, 889.

²⁶ See Carroll and Hubbard, *Bur. Stand. J. Research*, 1931, 7, 219.

²⁷ Sheppard and Hudson, *J. Amer. Chem. Soc.*, 1927, 49, 1814.

²⁸ Unpublished calculations by the author.

²⁹ Sheppard, *Phot. J.*, 1928, 58, 397; also Sheppard, Trivoli and Loveland, *J. Franklin Inst.*, 1925, 200, 51.

which develop without exposure. This may be due to the formation of oversized specks of silver sulphide which can, by themselves, induce development. The increase in \log itself also causes a drop in speed, but Carroll and Hubbard²² have shown that the two effects as mentioned are of different nature. We thus arrive at the conclusion that a slight increase in size of the silver sulphide speck will transform an optimum speck into a "log speck." In order to understand this, it is necessary to assume that the electronic energy levels in the speck deepen rapidly with increasing size of the speck. According to the original conceptions of Gurney and Mott,¹ development occurs if the levels of log specks are lower than those

of the developer, while those of the optimum size have their levels just above the developer levels (Fig. 3).^{*} The levels in a speck smaller than the optimum size are so near to the silver halide conduction levels that the speck forms a very inefficient electron trap.

FIG. 3.—Electron levels in silver halide, sensitivity speck, latent image, solid silver, and developer. (Illustrating Section IVa).

Thus we arrive at the conception of a sensitivity speck of reasonably small size which is comparable with the amount of latent image which might collect on it. A large amount of sensitising substance is required to form one optimum size speck by a process of chance aggregation. A log speck is only slightly bigger than one of optimum size; thus a slight increase in digestion will transform the latter into the former. It is felt that this conception of the sensitivity speck gets over the difficulty felt formerly when it was assumed²³ that all the sensitisier required per grain for optimum sensitisation went to make perhaps a single sensitivity speck, which would be of the order of 10^8 times as large as the latent image speck.

(d) Electric Capacity of Sensitivity and Latent Image Specks.

For more detailed considerations of latent image formation as become necessary when treating problems like reciprocity failure, it is of interest to know how many electrons can stay

on a sensitivity or a latent image silver speck at the same time, or how many electrons are likely to get into a speck under normal exposure conditions. There are two effects to be taken into account.

Firstly, an electric charge raises the potential of the speck so that further electric charges are repelled. Secondly, the walls of the "potential box" con-

No. of Molecules.	Radius of Sphere in Å. for		Potential Rise in Volts for one Electron Charge.	
	Ag	AgS	Ag	AgS
4	2.53	3.82	4.74	3.12
10	3.43	5.10	5.47	4.30
100	7.36	11.17	1.62	1.07
1,000	15.93	24.07	0.75	0.50
10,000	34.31	51.81	0.35	0.23

* Compare Section IV. The mechanism of development suggested in that section differs from the one implied here; in both cases, however, a larger sensitivity speck would cause a grain to develop as "log grain" without exposure.

stituting our speck become thinner. Thus an electron has a better chance of escaping from the charged speck, since it has a definite probability of penetrating a potential barrier, even if its energy is not sufficient to surmount this barrier (tunnel effect). The second effect is not easily treated quantitatively. The rise in potential of a speck is readily estimated, however, and has been worked out under the assumption that the specks are spherical and embedded in a dielectric of constant $\kappa = 12$. The potential on the surface of a sphere is given by $P = ne/kR$. For the data in the table, the radius of the sphere was so chosen that the volume of the sphere is identical with that occupied by the number of molecules in the normal crystal structure.

Even assuming that the sensitivity speck consists of 10,000 molecules, we find that a single electron charges it up to a voltage which requires an energy considerably in excess of average thermal energy to surmount $(3/2kT \approx 0.04\text{eV})$. We see that it is very unlikely for more than a single electron to be found on the sensitivity or the latent image speck at the same time.

IV. Development.

No clear picture of the mechanism of development is considered to have been presented so far. In considering the process of reduction of silver halide to metallic silver and halogen ions which constitutes development, the main question is : Which factor distinguishes the exposed from the unexposed silver halide grains ? All reliable evidence points to the suggestion that this factor is the presence or absence of the small silver speck, the formation of which we have considered in the previous sections. Whether this is correct or not, the latent image is, by definition, nothing but this distinguishing factor.

In all considerations involving chemical processes, in our case development, a sharp division must be drawn between features which will enable one to decide in which direction a possible reaction will go, and those which will merely influence the rate at which the reaction proceeds. Earlier workers regarded development as a reversible reaction in thermo-dynamic equilibrium : here pure energy considerations were made to account for the distinction a developer makes between exposed and unexposed grains. Present views regard this distinction as a difference in the rate of development. We shall deal with both points of view in turn, and try to evolve a mechanism that accounts for the known facts, realising that our knowledge is at present insufficient to decide whether any of the mechanisms so far suggested is correct. We shall be able, however, to exclude certain processes which have lately been suggested.

(a) Energy Balance.

Sheppard and Mees⁵⁰ already in 1907 suggested many of the views which are still being held on the processes involved in development, and reference should be had to their book also for earlier work. They consider that under certain conditions, development may be regarded as a reversible reaction in thermodynamic equilibrium. Careful experiments by Reinders⁵¹ have shown this to be correct under certain circumstances. In thermodynamic equilibrium, a solution to be able to act as a developer must have a redox potential lying between two well-defined limits.* If the redox

⁵⁰ Sheppard and Mees, *Theory of the Photographic Process*, Longmans, London, 1907.

⁵¹ Reinders, *J. Physic. Chem.*, 1934, 38, 784.

* The redox potential measures the reducing or oxidising power of a system, when the reaction is assumed to proceed in a reversible way, as in a galvanic cell. It may be described as the tendency of setting up a double layer on a metal electrode, and defined as $P = C/n \log .Ox/Re + E_0$, where Ox is the concentration of the oxidised, Re that of the reducing ions, and E_0 the electrical potential,

potential is too high, the solution acts as an oxidiser and dissolves the latent image, if too low, even the unexposed grains are developed. Reinders discussed the process on a model in which the silver halide was assumed to be dissolved and the reaction to take place in solution, in accordance with the supersaturation theory of development.²⁹ The supersaturated silver would then deposit on the latent image nuclei. Reinders' considerations are valid only under these assumptions. Development does not usually proceed according to these conceptions, since the individual grains are not dissolved, but reduced as entities. This means that the presence or absence of a latent image speck decides whether a grain is developed or not during the time the developer is allowed to act. The presence of a minute speck of silver cannot alter the energies involved in a reaction or the chemical affinities; all it can do is to effect the rate of reaction by acting as a catalyst. Thus, when we are dealing with the reduction of individual grains, considerations involving the redox potential cannot tell us anything concerning the discrimination a developer makes between exposed and unexposed grains, but only whether silver halide will be reduced or not in thermodynamic equilibrium.

This will be clearer if we consider redox potential in terms of electron levels. We can say qualitatively that a developer is a solution supplying electrons at a certain pressure which we can denote by an electron level, which is high, if the pressure is high, i.e. if the redox potential is low (Fig. 3). If the solution is brought into contact with a system, which itself can be described by an electron pressure, then electrons will flow in the direction from the higher level to the lower. Solid silver, the reduction product of silver halides, can supply electrons at a certain pressure; reduction of silver halide occurs if the reaction is given time, if the developer level is above that of solid silver (I in Fig. 3). A small speck of silver presumably has higher levels than a big speck; in Fig. 3 a latent image speck would be dissolved, i.e. oxidised by a solution with levels at I. All the same, the grain would be reduced in the long run by I: there is a very small probability that a local electron pressure higher than the average will be set up sufficient to start the reduction process. Once a solid speck of metal is formed, the reaction will proceed to completion. A solution with its levels at II will not, on the average, oxidise the latent image and can initiate the reduction process at once, which it cannot do on a grain without a latent image speck. It is likely that a grain is reduced immediately if a developer can supply electrons into the conduction levels of silver halide. The difference in energy between the conduction levels and a solid silver electrode corresponds to an activation energy which has to be overcome in order to initiate development in an unexposed grain if a developer like I is used; an exposed grain differs from an unexposed one by the existence on its surface of a catalyst increasing the rate of reaction. We shall see below that other surface conditions contribute to, or possibly play a decisive part, in the activation energy involved, but note that there appears to be some justification in Reinders' contention, that the rate of development must be influenced by the redox potential of the developer. Under usual conditions of development, the redox potential is considerably below that necessary to reduce silver halide; as a consequence, unexposed but unprotected silver halide crystals are reduced immediately.³⁰ The protection of the grains is afforded by the surrounding gelatine, as will be discussed under (b) below. In normal development, we never give the system time to reach equilibrium, and the reaction is not always reversible. In considering the mechanism of development, we thus get little help from

usually measured against a standard hydrogen electrode, when $Ox - Re$; n is the difference in the charge of the ions between the reducing and the oxidised form.

²⁹ Abegg, *Arch. wiss. Phot.*, 1899, I, 15; also ref.¹.

³⁰ Shoppard, *Phot. J.*, 1929, 69, 330.

thermodynamics, and have to look out for factors influencing the rate of reaction.

(b) Mechanism of Development.

Experiments on latent image distribution show that latent image is sometimes contained inside a grain, where a normal developer does not reach and where it can be used to develop the remainder of the grain, after its outer layers have been dissolved.²⁴ This finding precludes all those theories which regard as a latent image a change in the conditions of the original surface, say the charge of the grain, and the silver formed only as an accidental addition which, however, serves as an efficient condensation nucleus for any more silver formed.²⁵ The results on latent image distribution are regarded as one of the best indications so far available that the latent image consists of localised specks of silver, the others being the possibility of physical development after fixation, and the development of iodised grains. In this latter case, the whole of the, say, silver bromide grain becomes converted into silver iodide, the single crystal being changed into a porous polycrystalline mass. Thus, the developer can reach also the internal latent image, a large proportion of which survives this drastic treatment.

We shall consider two distinct processes by which the preferential reduction of silver halide grains carrying a latent image silver speck may proceed. In both models, development is regarded as a heterogenous chemical reaction, which is catalysed by the presence of the latent image so as to proceed at a higher rate.²⁶ Certain experimental facts on development are so important in this connection that we shall list them below.

The development of an individual grain can be divided into two periods, a period of induction, when no visible change occurs, and a period of visible reduction. Once this second period has begun, development proceeds at roughly the same rate for any one developer. Individual grains differ in the main by the length of the induction period.²⁷

This statement does not imply that the curve in which density is plotted against time of development, necessarily shows an induction period. It has been shown that an induction period occurs only with those developers in which the reducing chemical occurs in ionic form. With neutral developing molecules, the density-time curve goes straight through the origin, where the slope is greatest.²⁸

The rate of development of exposed grains can be influenced considerably by impurities, as for example, certain dyes, which are probably adsorbed by the grain surfaces.²⁹

Developed silver occurs as a rule in the form of a tangled mass of ribbon-like filaments,³⁰ giving the "overwhelming impression that the silver filament is formed by ejection from the silver bromide crystal."³¹

(1) Electrolytic Mechanism of Development.—Gurney and Mott³² had suggested a mechanism of development, which forecasts the production of silver ribbons. The latent image was regarded as an electrode which accepts electrons from the developer and then attracts interstitial ions from the silver halide lattice, in analogy to the mechanism of latent image formation. In this way, the original latent image is pushed out from the grain by the new silver forming underneath in the form of a thread. Many

²⁴ See, e.g., Schwarz, *Phot. Korr.*, 1933, 69, 27.

²⁵ Volmer, *Z. wiss. Phot.*, 1920-21, 20, 189.

²⁶ See Moedinger, in Hay's *Hdb. d. Photographie*, Vol. V, p. 271, Wien, 1932.

²⁷ James, *J. Physic. Chem.*, 1939, 43, 701.

²⁸ See James and Kornfeld, *Chem. Rev.*, 1942, 30, 1.

²⁹ Scheffler, *Brit. J. Phot.*, 1907, 54, 116, 231; Hall and Schoen, *J. Opt. Soc. Amer.*, 1941, 31, 281.

³⁰ Mees, *Scient. Monthly*, Oct., 1942, p. 293; *Nature*, 1942, 150, 720.

objections have been raised to this conception,^{27, 28} according to which the rate of development is limited by the rate of formation of fresh interstitial ions. It was shown in Section II (c) (1) that the rate of formation of new ions is much too slow to account for the normal rate of development.

This model can be modified, however, so that the rate of development can be accounted for; the new hypothetical picture has not been checked with experience. Imagine a latent image speck charged to capacity by electrons from the developer. First of all the mobile interstitial ions will go up to the speck and discharge some of the electrons. This will take of the order of 10^{-6} seconds.¹⁶ Because of the slow rate of formation of new interstitial ions, this process soon comes to an end, certainly with silver chloride grains. A different mechanism now comes into play. The field set up by the charged and by now somewhat enlarged latent image will pull out some of the nearest silver ions from the lattice. The heat produced in development will assist in this process. The holes so formed will be "repelled" by the charged silver speck and the holes near the latent image will be filled up by neighbouring silver ions (II (c) (1)). Thus the process can be repeated. The holes will accumulate on the parts of the crystal removed from the growing silver speck; in other words, there will accumulate on the surface a surplus of bromine ions, which are taken up by the water surrounding the grain. It will be seen that this process

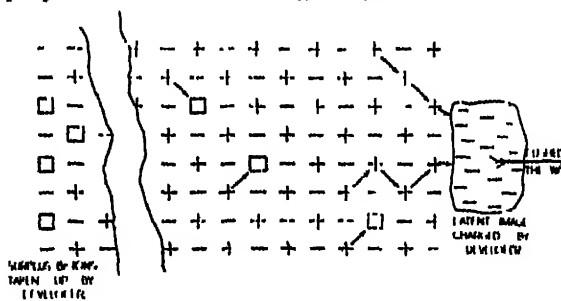


FIG. 4.—Electrolytic mechanism of development.
□ are places where + ions are missing.

amounts to a dissolution of the crystal, all the moving of the silver ions, however, taking place in the solid, the bromine ions not being required to move through the lattice. It is important to realise that the rate of development cannot be determined by any considerations on

the lattice and other energies involved: a breakdown of the silver halide structure is an essential feature of development, whatever the mechanism. The activation energy involved in the movement of the holes is quite small and cannot therefore constitute the determining factor. The rate of development is probably determined by the surface conditions of the grain, as discussed below. In the process suggested here, silver is deposited on the side of the original latent image facing the silver halide crystal; the latent image and any silver formed previous to the time considered will at any moment be pushed out of the body of the crystal in the form of a thread. The process is illustrated in Fig. 4.

It is obvious to suggest that the second stage of development will set in only if the silver speck has reached a certain critical size as the result of the first stage, although no valid justification can, at present, be given for this assumption. If the assumption is made, however, several hitherto puzzling features of development can be accounted for, some of which are discussed below.

Induction Period.—On our model, the induction period in the development of a single grain occurs because in the first stage of development the silver speck does not necessarily grow to the full size necessary to initiate the second stage, simply by using up all the interstitial ions originally present. Thus there is a time interval during which the silver speck grows slowly at the rate at which fresh interstitial ions are formed, until the critical size is reached when the second, more rapid stage of reduction sets

in. Romer⁴¹ has suggested that the length of the induction period is a decreasing function of the size of the original latent image speck.

It should be pointed out, however, that the induction period may be accounted for in several other ways. For example,⁴² the rate of an autocatalytic reaction will at first increase with the amount of catalyst present, and will, on the whole, be S-shaped. The induction period may therefore be nothing but the initially slow rise of the reaction curve. On this score, there is therefore no need to assume the existence of two separate processes in development. Latent image specks buried in the silver halide would also cause a genuine induction period : it would take some time for the solvent action of the developer to dissolve the silver halide layer covering the latent image. This consideration shows that investigations on the kinetics of development should not be carried out using a developer containing silver halide solvents.

Sensitivity of Large Grains.—A large grain containing a single sensitivity speck will be more sensitive than a small one, not only because of its larger target area to light, but also because it contains a larger total number of interstitial ions to begin with. Thus, the latent image speck can grow to the critical size for the second stage with a smaller original latent image speck than would a speck attached to a smaller grain ; the rate of reduction becomes sufficiently high to cause the grain to be reduced before development is interrupted.

Iodo-bromide Emulsions.—It is a well-known fact that the sensitivity to light of an iodo-bromide emulsion is considerably higher than would be expected merely from the change in spectral absorption. There appear to be two possible reasons for this increase in sensitivity. First, the number of interstitial ions may increase if an impurity as, for instance, silver iodide is added to a pure silver halide crystal. Thus, in the first stage of development a speck will grow to a larger size, in an iodo-bromide grain. Secondly, the distortion of the structure by the iodine ions is very likely to lead to a loosening up of the structure, so that fresh interstitial ions are formed more rapidly. Thus, there seems to be good reason to assume that a speck sufficient to initiate the second stage of development can be obtained from a relatively small original latent image speck for an iodo-bromide grain.

(2) Development: an Interface Catalysed Reaction.—James and Kornfeld⁴³ have pointed out that development may not be as mysterious a process as is often made out : it falls into the general class of heterogeneous reactions, catalysed by the presence of one of the reaction products,⁴⁴ and occurring at the boundary where the three components, *viz.* silver halide, metallic silver, and developer, meet. The silver ions in the silver halide are regarded as being "adsorbed" to the silver, this adsorption being the essential preliminary for the metallic silver to be able to catalyse the reaction, *i.e.* to increase the rate of reaction by lowering the activation energy required. The reaction is assumed to proceed along cracks and flaws of the silver halide, the silver being produced in the form of filaments for that reason.

In spite of many virtues of this conception, the explanation of the form of the developed silver is not very satisfactory ; it would be surprising if cracks and fissures were present in sufficient regularity to account for the even threads formed.⁴⁵ On this conception one would rather expect to find sheets of developed silver. Experiments on crystal growth may, however, account for the shape of the developed silver. We have to consider that the sides of the latent image and of the developing silver facing the surrounding gelatin may be contaminated so as to stop the growth of the single crystal of silver the thread most likely represents. Growth may occur only on the fresh faces, along which freshly formed

⁴¹ Romer, *Przegnyst Chemiczny*, 1934, 18, 533.

silver atoms are probably quite mobile for a short space of time.⁴² The new silver atoms, even if formed on the edge of the silver, may thus attach themselves anywhere on the silver-silver halide interface. There is thus no need to assume a movement of the triple interface, where reaction occurs, in particular when the possibility is considered that by the process discussed in Section II (c) (1) the "holes," formed by the reduction of surface silver ions may be filled up rapidly by ions from within the crystal.

(3) Rate of Development.—Photographic emulsions are usually prepared in the presence of a surplus of halogen ions, so that the grain surfaces carry a stoichiometric surplus of negative ions. This surplus is neutralised electrically by adsorbed positive ions; the grains thus carry an electrical double layer, negative side inwards, the effect of which is to hinder negative ions in the solution, or electrons in reaching the silver halide.⁴³ Gelatin also appears to become adsorbed to the surfaces of the grains.⁴⁴ Both types of protective layers thus retard development of grains. The increase in the rate of development brought about by the presence of the latent image can be considered as due to a weakening of these protective layers by the latent image silver: on one view, the increase in reaction rate by silver allows reaction to occur when contact between developer molecules and silver ions at the triple interface is of short duration; on the other, the silver acts as an electrode accepting electrons, conducting them through the protective layers to the silver ions underneath. It will be seen that these two views are not as divergent as may appear at first sight; on both the condition of the surface of the grain and the latent image silver plays a big part in determining the rate of reaction, both by mechanical and electrical inhibition. It must be realised too, that the double layer covering the silver and that covering the silver halide are intimately connected and probably in equilibrium: anything we do to one, say by increasing the bromide ion concentration resulting in a strengthening of the layer over the silver halide, will similarly affect the other. This coupling must be particularly efficient in view of the minute dimensions of the latent image compared with the parent silver halide crystal: a double layer on the crystal electrically covers also the latent image.⁴⁵ It is for this reason that experiments on the preferential adsorption of substances on either silver or silver halide can hardly be expected to decide between the two models under discussion. Evidence on the adsorption of hydroquinone on silver⁴⁶ has been refuted,⁴⁷ but the amounts which would be expected to be adsorbed are within the experimental errors.

To sum up, we seem to be unable to decide between the two mechanisms of development proposed, either by considerations of the energies involved, or of the factors influencing the rate of reaction. Perhaps it is permissible to say that the squirting out of the developed silver from the silver halide as visualised in the electrolytic mechanism provides a less forced account of the threadlike appearance of the developed silver.

V. Photographic Effects.

The usually simultaneous occurrence of electronic and ionic processes in the formation of the latent image manifests itself in various ways. Since the time and temperature constants of the two processes differ widely, exposures of different duration and intensity and obtained at different temperatures often give widely differing results; in some cases it has been found possible to obtain a certain separation of the processes in time and thus to study them to some extent individually.

⁴² Volmer, *Trans. Faraday Soc.*, 1932, **28**, 359.

⁴³ Gurney, *Ions in Solution*, Cambridge, 1936.

⁴⁴ Rabinovitch, *Trans. Faraday Soc.*, 1938, **34**, 920.

⁴⁵ Perry, Ballard, Sheppard, *J. Amer. Chem. Soc.*, 1941, **63**, 2357.

(a) Reciprocity Failure.

The photo-chemical reciprocity law states that the same product of intensity of light and exposure time, $I \times t$, will produce the same effect, no matter what the individual values of I and t . This law holds if the reaction constitutes a single stage process and would therefore not be expected to hold for the case of photography, where a double stage process is involved. The failure of the reciprocity law is usually demonstrated in a reciprocity failure curve, in which the log. exposure necessary to produce a constant density on processing is plotted against the log. intensity. This curve often exhibits an optimum, and we speak of low intensity failure at intensities lower, and of high intensity failure at intensities higher than the optimum intensity, although the causes of both operate on either side of the optimum.

(1) Low Intensity Failure.—It has been pointed out already that a very small speck of silver is unstable, because its electrons are but loosely held. If electrons escape, the silver ions thus left on the speck will go into the lattice into interstitial positions.¹ This disintegration will go on also during latent image formation and will cause the process to be less efficient at low than at high intensities. Webb and Evans⁴⁶ deduced that a latent sub-image speck* is stable when it has reached about half the size necessary to make a grain developable. After stability has been reached, the speck builds up equally efficiently at low as at high intensities of light. The ratio of the amount of latent sub-image to image specks is generally higher, the higher the intensity of light used. This is because at higher intensities the growing specks quickly and efficiently reach the stable size, whereas they do so but slowly and inefficiently at low intensities. Thus, as soon as the stable size is reached at low intensities, it will be built up to the latent image size, making full use of all the electrons formed. The inefficiency of sub-image formation, then, is the cause of low intensity reciprocity failure, as was realised already by Weinland.⁴⁷

(2) Pre- and Post-Exposure.—The fact that the sub-image growth is inefficient, that of the subsequent image growth fully efficient is of some practical importance. If an under-exposed picture is taken at high intensities, there will be a large amount of sub-image present, which normally cannot be developed. A low intensity uniform post-exposure will bring the sub-image up to the developable size, thus acting as an auxiliary method of development.⁴⁸ If the intensity of the post-exposure is low enough, no new sub-image will be formed, and thus no additional fog produced. In practice, this ideal case is often not obtained. The main reason probably is that the sub-image is not always absolutely stable, but has been found in certain cases to be subject to fading with time.⁴⁹ Thus there is a limit to the exposure time that can usefully be applied for the second exposure, and a certain amount of sub-image and thus latent image will always be produced. It should be pointed out that the practical result obtained will depend on the emulsion properties.

The effect described of adding a short high intensity and a long low intensity exposure can also be used to record an under-exposed low intensity picture.⁵⁰ With many emulsions a uniform pre-exposure at high intensities produces a large amount of sub-image, which is built up to the latent image size only in those areas where the additional low intensity exposure in the picture is sufficiently large. The second picture exposure

⁴⁶ Webb and Evans, *Phot. J.*, 1940, 80, 188.

* A stable speck which is below the size necessary to make a grain developable will be designated as a (latent) sub-image (speck).¹

⁴⁷ Weinland, *J. Opt. Soc. Amer.*, 1927, 15, 337; 1928, 16, 295.

⁴⁸ Moore, *Phot. J.*, 1941, 81, 27.

⁴⁹ Unpublished experiments by Berg and Burton.

must be given soon after the sensitising exposure, otherwise the sub-image may fade away.

Since post-exposure at low intensities may be regarded merely as a method of developing the sub-image, it enables the growth of the sub-image to be traced.⁴⁹ This is best done by plotting density (above log) against exposure (not log, exposure) on a time scale. It was found that the $D-E_t$ curve without post-exposure exhibits a pronounced "toe," i.e. a period where slope increases with exposure time. A sufficiently post-exposed curve, however, goes through the origin and is straight up to densities of the order of 0.2 to 0.3. If it is permissible to regard the grains forming densities near the threshold to be of one class as to size and sensitivity, a toe on a density-time curve means that the latent density formed in an interval of time δt depends on the previous exposure: the toe is a manifestation of the existence of the sub-image which lasts for some time, influencing the rate at which density increases with time, and the cumulative growth of the latent image. On the other hand, a straight line $D-E_t$ curve indicates that the density increase in δt does not depend on the previous exposure history, but only on the exposure in δt . Thus it appears that the sub-image is not subject to a process of gradual growth, but is formed instantaneously. The condition for its formation appears to be that a certain minimum number of quanta is absorbed by the grain in a certain maximum short interval of time. Reciprocity failure would then manifest itself as a change in slope of the post-exposed $D-E_t$ curve. The number of quanta and the time interval required to form the sub-image will determine the rate of change of slope with varying intensity. For a single-quantum process, as in the case of X-ray exposures, there is no reciprocity failure and the slope of the $D-E_t$ curve does not vary with intensity.⁵⁰

It is a moot point whether the instantaneous formation of the sub-image demonstrated means that no silver speck is formed until a certain concentration of electrons is set up¹ or that silver is actually formed as soon as any electrons are liberated, and that the small speck so produced evaporates very rapidly.⁴⁹ To sum up, we can describe low intensity reciprocity failure as being brought about by the necessity of a grain absorbing a certain number of quanta within a certain interval of time in order to produce a sub-image. Once the stable sub-image is formed, further electrons liberated by light are used efficiently.

It is clear that this picture of low intensity failure is not complete. What happens to the electrons that are not made use of at low intensities? There must be a mechanism of recombination or trapping of electrons which so far has not been studied or understood.

(3) **High Intensity Reciprocity Failure.**—High intensity reciprocity failure seems to be fairly well understood. At high intensities there is no difficulty in obtaining the necessary number of quanta absorbed in the critical interval of time; here the limitation lies in the limited electric capacity of the sensitivity specks. The movement of electrons is very rapid, while the movement of silver ions takes more time so that the charged sensitivity speck is not neutralised immediately. While this state persists, any further electrons will be repelled, so that a concentration of electrons is set up in the grain. This might have two effects: either the condition for sub-image formation as set out above might become fulfilled for a shallow trap existing in the grain, or the electrons might cause a local lattice breakdown and consequent formation of a silver speck. Which of these alternatives describes the mechanism correctly, we do not know. The experimental evidence is that at high intensities, latent image is formed inside the grain, the more the higher the intensity.⁵⁰ High intensity failure is thus characterised by a change in latent image distribution; there is no experimental evidence to suggest that the total amount of silver

⁴⁹ Glocker and Traub, *Physik. Z.*, 1921, 22, 345.

formed is less at high than at optimum intensity. It can be shown that high intensity failure occurs in the main in the second stage of latent image formation, sub-image formation not being subject to high intensity failure, as is evidenced by the finding that high intensity failure can be eliminated by a low intensity post-exposure.¹⁰

(4) **Very High Intensities.** - At very high intensities a state of affairs should be reached where the electronic and ionic processes cannot be separated in time any further by shortening the exposure time: the electronic process is practically instantaneous, its first stages being over before the ions have time to move appreciably. From a certain time of exposure onwards towards shorter times still the process of latent image formation will run in an identical manner: reciprocity failure should be absent. This has actually been found to be the case. At an exposure time of about 4×10^{-8} seconds, the reciprocity failure curve of all materials tested bent over into the horizontal.¹¹ The position of the bend-over point can be shown to depend on the mobility of the ions which varies with temperature as $e^{-E/kT}$. This is confirmed experimentally.

(5) **Temperature Effect on Reciprocity Failure.**—Reciprocity failure at ordinary intensities also varies considerably with temperature.¹² The temperature effect can be accounted for, at least qualitatively, on the basis of the mechanism described. The drop in ionic mobility at reduced temperature responsible for the shifting of the bend-over point of the reciprocity curve towards longer times of exposure also affects the branch of the curve at the high intensity side of the optimum: at low temperature, repulsion of electrons from a sensitivity speck occurs at a time of exposure where at normal temperature the mobility of the ions is quite sufficient for some of the electrons to be discharged during the exposure. Thus, at reduced temperatures, the whole high intensity branch is shifted towards longer times of exposure, and by the same argument, towards shorter times for elevated temperatures.

Low intensity failure is similarly affected, but for a different reason. Here the stability of a small speck of silver depends on temperature, the probability of an electron being lost from a speck in a time interval depending on temperature as $e^{-W/kT}$. Thus the low intensity branch of the reciprocity failure curve also shifts towards longer times of exposure with decreasing temperature. The temperature coefficients of high and low intensity failure being different, one would expect some change in shape in the reciprocity failure curve as the temperature drops; the most important effect, however, is a bodily shift of the whole curve towards longer times and lower intensity, as the temperature is decreased, and towards shorter exposures, as temperature is increased.

(b) Low Temperature Exposures.

If the temperature is dropped sufficiently, the flat high intensity end of the reciprocity curve will occupy the whole range of exposure times practicable: reciprocity failure disappears entirely at sufficiently low temperatures.¹³ That means we can now separate entirely part of the electronic from the ionic process: at sufficiently low temperatures ionic mobility drops practically to zero. It has been found possible to obtain a certain amount of information on the electronic process in this way.

At low temperatures (90° K.) a very much larger amount of internal image is formed relative to the surface image than, say, at the optimum of the reciprocity failure curve at room temperature.¹⁴ There is, as would be expected, a change in latent image distribution as the temperature is reduced in a similar direction to that occurring as the intensity is increased. Thus the speed for the surface latent image is considerably reduced at low

¹⁰ Webb, *J. Opt. Soc. Amer.*, 1935, 25, 4.

¹¹ Berg and Mendelsohn, *Proc. Roy. Soc. A*, 1938, 168, 168; Evans and Hirschlaif, *J. Opt. Soc. Amer.*, 1939, 29, 164.

temperatures. That for the internal latent image is not increased, however, and, in fact, drops slightly as the temperature is dropped to 90° K.; internal speed at these low temperatures is always lower than that at room temperature, however short the exposure of the latter. It is thus clear that the change in latent image distribution found does not account entirely for the behaviour of photographic materials at very low temperatures. Various other findings point the same way. Thus, both the contrast and the maximum density of the surface image are considerably below those obtained for brief times at room temperature. Furthermore, an additional change in contrast and maximum density occurs, as the temperature is dropped from 90° to 20° K.,⁵³ although ionic mobility is already completely arrested at the higher of these temperatures. It thus appears that there is an additional cause responsible for the drop in speed operative at very low temperatures. It may be that at these temperatures trapping of the electrons occurs in close proximity to the bromine atoms from which they were released. Photo-conductivity should also drop at these temperatures; the experimental evidence on this is, however, contradictory.¹ If this drop occurs at all one would expect to find it at temperatures between 20° (liquid hydrogen) and 4° K. (liquid helium). Experiments showed that photographic sensitivity at 4° K. is of the same order as that at 20° K.⁵⁴ It appears, therefore, that the loss in photographic sensitivity at low temperature cannot at present be completely accounted for.

Experiments were done in order to explore further the fate of the electrons while the photographic material is held at low temperature.⁵⁵ It is clear that the electrons must be held trapped somewhere in the crystal, because if they were free to move they would recombine with the bromine atoms whence they came. There are two possible ways in which electrons can be trapped in such a way as to be able to contribute to the latent image: either they are trapped in the sensitivity specks themselves,⁵⁶ or in other traps which are shallow enough to release the electrons when the emulsion is warmed up. When that occurs, both the electrons trapped in the shallow traps and the silver ions in interstitial positions become free and the latent image is formed.

There is experimental evidence for both kinds of traps to be operative. Of this evidence only one fact need be mentioned here. The low temperature latent density, which consists of trapped electrons, can be bleached out very effectively by red light, if the material is kept at low temperature all the time.^{54, 56} After warming up and re-cooling, this is no longer possible.

One would thus conclude that the red exposure lifts the electrons from the traps when they will either be trapped afresh or recombine. The bleaching effect shows that bromine atoms are still available while the material is kept cold. If the material is exposed to radiation containing a proportion of actinic as well as bleaching light, one would expect that a state of equilibrium where equal numbers of electrons are liberated and lost in a unit of time be established for continued exposure, if there were only one kind of trap. Actually a latent density exposed to mixed actinic and bleaching radiation decreases to a minimum and then increases again. This indicates that a number of electrons has been transferred to deeper traps from which they cannot be liberated by red light. An investigation into the spectral sensitivity of the bleaching effect shows that the deep traps must be between 1 and 2 e.v. deep since bleaching does not occur on continued exposure with quanta of this energy. On the other hand, it can be shown that the shallow traps cannot be deeper than 0.8 e.v., otherwise the electrons would not become freed at room temperature. Room

⁵³ Berg and Mendelsohn, *Proc. Physic. Soc.*, 1937, 49, 38.

⁵⁴ Berg, *Trans. Faraday Soc.*, 1939, 35, 445.

⁵⁵ Webb and Evans, *J. Opt. Soc. Amer.*, 1938, 28, 249.

temperature is thus incapable of freeing the electrons from the deep traps. In order that the electrons in deep traps can contribute to the latent image, it is necessary to assume that the deep traps are the sensitivity specks themselves.⁵⁴

The mechanism of latent image formation at low temperatures can thus be summed up as follows: The exposure liberates electrons which move about in the conductivity levels until they are trapped. There are deep traps of 1 to 2 e.v., which constitute the sensitivity specks, and shallow traps of less than 0.8 e.v. from which latter the electrons are released on warming up. The frozen-in ions in interstitial positions and the bromine atoms then also become mobile, and the latent image forms in the usual way. The assumption that bromine atoms become frozen in at low temperatures is essential to an understanding of low temperature photographic sensitivity but is in contradiction with the considerations in II, c. 2. There is no independent experimental evidence on this point.

(c) Various Photographic Effects.

A theory on latent image formation should account for all the different photographic effects. In what follows a small selection of effects is treated, chosen in the main because they fit in easily into the picture given without many additional hypotheses.

(1) **Clayden Effect.**—A very high intensity (spark) pre-exposure desensitizes the photographic material towards a subsequent exposure at lower intensity. The high intensity exposure produces a certain amount of internal latent image and sub-image, both of which act as electron traps competing with the surface sensitivity speck for the electrons produced by the lower intensity exposure. This is proved by the finding that the desensitising effect for the surface latent image is accompanied by a sensitising effect for the internal image.⁵⁵ A similar effect occurs if a low temperature exposure is followed by one at room temperature, bearing out the analogy between low temperature and high intensity room temperature exposures.⁵⁶

(2) **Solarisation.**—With many photographic materials, increase in exposure eventually leads to a drop in developed density.

This effect can be removed by treating the emulsion with a halogen acceptor before exposure;⁵⁷ it is caused by the bromine atoms which leave the silver halide grains. For big exposures there is sufficient bromine present all around the emulsion grain to attack the latent image silver and form a coating of silver halide over it through which a normal developer cannot act. Thus solarisation occurs only in the surface latent image,⁵⁸ and can be removed by treating the material with a silver halide solvent like hypo for a brief time.⁵⁹

(3) **Dye Sensitisation.**—In order that a dye shall act as a sensitising dye, its molecules must be adsorbed to the silver halide.⁶⁰ The absorption spectrum of the dye is altered by the adsorption process, and it has been shown that the spectral sensitivity of the emulsion corresponds to the absorption curve of the adsorbed dye.⁶¹ A further obvious requirement of a sensitising dye is that its excited electron levels shall lie above the lowest of the conduction levels of the silver halide. If this is the case, the excited electron can pass readily from the dye molecule into the crystal, and form latent image in the ordinary way. Further requirements of sensitising dyes, as, for example, planar structure, which enables aggregates of edge-on adsorbed molecules to be formed on the crystals, and co-planar

⁵⁵ Abney, *Instruct. in Photogr.*, London, 1882.

⁵⁷ Nafe and Jauncey, *Phys. Rev.*, 1940, 57, 1048.

⁵⁸ Sheppard and Crouch, *J. Physic. Chem.*, 1928, 37, 751.

⁵⁹ Leermakers, Carroll and Staud, *J. Chem. Physics*, 1937, 5, 878; Leermakers, *ibid.*, 5, 889.

coupling of electronic displacements in the dye and a congruent plane of the silver lattice have been discussed recently.⁶⁰

The mechanism of latent image formation, apart from the absorption act, is identical in the dye sensitised and the normal spectral sensitivity regions. This has, for example, been demonstrated by experiments on latent image distribution, which is identical provided the same density is produced by an exposure of the same duration,⁶¹ and is borne out further by the fact that reciprocity failure curves for different wavelengths are parallel, if plotted against time of exposure;⁶² no doubt they would be identical if it were possible to plot the curves not in terms of (visual) intensity, but of number of quanta absorbed.

All these results indicate that there is no essential difference in latent image formation, whether the electrons come from bromine ions or dye molecules. This is considered to support the view that normally photographically effective absorption of light in the long wavelength tail of the main absorption band (IIa) takes place on the surface of the grain. If it did not, it would be difficult to understand why the presence of bromine atoms all over the interior of the grain should not manifest itself as a change in latent image distribution with change in wavelength of light, as surface absorption in the dye sensitised region is changed to volume absorption in the natural sensitivity region. It appears to be a useful working hypothesis that all photographically effective absorption occurs on the surface of the grains.

It has been shown that one dye molecule can be responsible for the successive production of as many as 50 electrons.⁶³ This means that either by an as yet not understood mechanism the molecule regains its electron, or that the dye does not actually lose an electron, but passes its excitation energy on to the nearest bromine ion. The energy deficit in the latter case would have to be supplied by thermal energy at the moment of energy transfer, in the former from the same source, but at some time after the electron has been transferred from the dye to the crystal. In any case, supply of thermal energy appears to be an essential condition for the mechanism of dye sensitisation, and one would expect a breakdown of dye sensitisation at sufficiently low temperatures. This was found with some dyes, but not with others.⁶⁴ No systematic investigation has been made along these lines, and the riddle of the mechanism of dye sensitisation remains. It may be justified to suggest that previous results with one or two dyes have been generalised too much. Thus it is possible that with some dyes, several electrons can be produced successively from one dye molecule as discussed above and that these dyes are very sensitive to changes with temperature. Those dyes which are not so sensitive to temperature changes, may be supposed to be able to supply one electron only, and then become permanently decolorised.

The writer wishes to put on record his personal indebtedness to Professor N. F. Mott, and to his colleagues, both in this laboratory and that of the Eastman Kodak Co., in Rochester, engaged or interested in latent image research. Many of the views presented here are the results of formal and informal discussions spread over the last five years. It is therefore impossible to give individual acknowledgement for all the suggestions and ideas that have been incorporated in this paper.

⁶⁰ Sheppard, Lambert, Walker, *8th Congr. of Chem., Roma, 1938*, I, 273; *J. Chem. Physics*, 1939, 7, 263, 426; 1941, 9, 90.

⁶¹ Webb, *J. Opt. Soc. Amer.*, 1933, 23, 376.

⁶² Leszynski, *Z. wiss. Phys.*, 1926, 24, 261; Tellert, *Z. physik. Chem. A*, 1929, 140, 355; Eggert and Blitz, *Trans. Faraday Soc.*, 1938, 34, 892.

⁶³ Sheppard, Wightman and Quirk, *J. Physic. Chem.*, 1934, 38, 817; Ungar, *Z. Physik*, 1937, 106, 322; see also ref.⁶⁴. In all the above cases, there is a breakdown of dye sensitisation. This does not appear to be the case in the paper by Webb and Evans (ref.⁶⁵).

REVIEWS OF BOOKS.

The Chemical Aspects of Light. By E. J. BOWEN, F.R.S. (Oxford University Press, 1942. Pp. vi + 191. Price 12s. 6d.)

Mr. Bowen has performed a valuable task with distinction in writing this introduction to some of the more interesting problems of chemical physics. The book has deliberately been written with the object of presenting various problems non-mathematically, and in this it has largely succeeded. The more serious student who wishes to pursue in research or in reading any of the subjects dealt with will find the fundamentals put before him in this volume in a way that is both attractive and extremely helpful.

The first two sections of the book are concerned with waves and matter, light and light sources. The following section considers the absorption and emission of light, particularly in relation to the spectra of free atoms and molecules. The fact that such a wide range is covered in little over a hundred pages indicates both the art of compression and its dangers. Those who are not already familiar with the fundamentals of optics and spectroscopy will be able to amplify this survey from other well-known sources. Sections four and five are concerned with the transformation of absorbed radiation (fluorescence) and with the luminescence of solids. One or two small criticisms in the latter chapter may be mentioned. The phosphorescence of ruby is not, as stated, of very short duration, but lasts for a number of milliseconds; in this respect it is similar to the uranyl salts in duration of afterglow, but different from the tungstates and platinocyanides. Zinc orthosilicate activated by manganese impurity has a green and not a blue luminescence, and much work of recent years has shown that this phosphor photoconducts.

Later sections of the book consider such widely different phenomena as photosynthesis in plants and the photographic process; reactions of the eye to light; photocells and chemiluminescence. There are a number of appendices dealing with filters for discharge lamps, photochemical technique and preparation of phosphors.

The list of references is intentionally not very extensive, but an attempt has been made to include those giving surveys of the subject-matter concerned.

Much of the subject-matter and contents of Mr. Bowen's volume form the stock-in-trade of many physical chemists. We feel sure, however, that there are many research workers in this field, as well as students working for degrees, who will find this volume both readable and stimulating to an uncommon degree.

The punctuation would appear to require revision in a number of places.

J. T. R.

The Theory of Emulsions and their Technical Treatment. 4th Edition.

By WILLIAM CLAYTON. (J. and A. Churchill, Ltd., London, 1943. Price 42s. Pp. vii + 492.)

An enormous capital is involved in the industrial application of emulsions. This fact, together with the unsatisfactory scientific approach, until very recently, to the study of emulsions, has led industry to formulate

a series of cooking book recipes of semi-secret nature, built up by empirical practice. The nature and stability of emulsions and the phenomenon of phase inversion have even in the latest textbooks on these subjects been described as mysterious; it is deplorable that knowledge of a simple phenomenon, used by Nature and by Industry on a large scale, should only just be emerging from empirical practice.

The fourth edition of Dr. Clayton's book goes a long way to remedy this position. He realises how the advances in knowledge of the physical chemistry of phenomena occurring at interfaces, especially those occurring at the oil/water interface, ever since Langmuir's conception of orientation of molecules at the air/water interface in 1917, are helping to elucidate the problems of emulsions and their technical applications. The book includes an excellent survey with very full references to the latest scientific work on the structure and nature of interfacial films, and solid particles at interfaces; the substances used as emulsion stabilising agents which compose these films, their electrical, hydration and dispersion properties, the interfacial viscosity and the viscosity of the emulsion phases, together with the latest work on particle size distribution and adsorption of ions and protection against ions by protective colloids, etc., also reactions taking place at the interface and membranes composing special interfaces. Dr. Clayton gives an unbiased view of all the theories relating to the stability of emulsions and the phenomenon of phase inversion showing how each is contributing to the building up of a clear picture of the subject as a whole. He gradually merges all this scientific work into its technical implications giving a very comprehensive list of patents for each industry involved. The book likewise includes a description both of the instruments used in the scientific work and technical machinery used in preparing emulsions. It is to be expected that with the advance of the scientific treatment of emulsions which this book gives, a great improvement will take place in their technical application and new uses will be found for them, especially in the technical biological fields of food and agriculture.

The large number of new emulsifying agents which have been made available to the research chemist by the emulsion industry is proving invaluable for many problems in Colloid Chemistry, and it gives a source of supply of pure chemicals which would normally be very difficult to come by. Most of these agents are also of considerable biological interest. These substances are listed in the references under the heading of "Complex organic emulsifying agents"; this elucidates the chemistry of many of the substances usually only known by trade names.

It is a pity that this book, which besides its industrial uses is also of great interest to the research worker, should be priced at a figure (of 42s.) outside his usually modest finance. It is, on the other hand, well bound and printed on exceptionally good paper.

J. H. S.

THE BEARING OF THE DISSOCIATION CONSTANT OF UREA ON ITS CONSTITUTION.

By J. BELL, W. A. GILLESPIE AND D. B. TAYLOR.

(From the Department of Physiology, Trinity College, Dublin.)

Received 18th January, 1943.

The degree of hydrolysis of the salt of a weak base and a strong acid in aqueous solution can be determined by estimating the free acid in solution. In most cases, since the extent of hydrolysis is small, the free acid is present at a sufficiently low concentration to be regarded as having an activity coefficient of unity, and hence can be determined by the various methods available for the measurement of hydrogen ion concentration. Thus Walker and Wood,¹ by measuring the velocity of hydrolysis of cane sugar and of methyl acetate under the influence of HCl in the presence of urea (0.5 M) estimated the degree of hydrolysis of urea hydrochloride. From these results the authors have calculated the following values (Table I) for the hydrolysis constant K_h (25° C.) by means of the equation

$$\frac{[\text{base}] \times [\text{acid}]}{[\text{unhydrolysed salt}]} = K_h.$$

TABLE I

Molar Concentration of Urea.	K_h .
I	0.78
0.5	0.74
0.25	0.75
0.2	0.75
0.1	0.86

TABLE II

Solution.	Urea Concentration in 0.1 N HCl.	Electrode Potential (millivolts).
I.	0.1 M	388.9
II.	0.2 M	386.4
III.	0.3 M	384.3
IV.	0.4 M	382.1
V.	0.5 M	379.9

Making use of the more accurate electrometric methods now available, the question has been reinvestigated. By using several molecular proportions of urea in excess, easily measurable buffering was produced and the experimental error rendered less. Hydronium dissociation constants of urea were determined instead of hydrolysis constants of urea hydrochloride.

Experimental.

Hydrogen ion concentration was determined by the quinhydrone electrode used in conjunction with a 3.5 normal calomel electrode, the voltage being determined on a Cambridge Instrument Company slide-wire potentiometer, standardised by a certified Weston cell. The measurements were made at 21° C.

A series of five solutions (I, II, III, IV and V) was prepared, all deci-normal with respect to HCl and each containing a different molecular proportion of urea. The potentials of these solutions were determined with the quinhydrone electrode, and are shown in Table II.

¹ Walker and Wood, *J. Chem. Soc.*, 1903, 83, 484.

From these readings the amount of HCl buffered by the urea was determined by the following procedure. Small known volumes of 0.2 N NaOH solution were added to 50 c.c. of 0.2 N HCl and the mixture diluted in each case to 100 c.c. The quinhydrone electrode potentials of these solutions were measured with the identical apparatus and under the same conditions as before. The amount of HCl neutralised in each solution was readily calculated from the volume of NaOH added. In this way a series of readings was obtained connecting the electrode potential with the amount of HCl neutralised (Table III).

From a large-scale graph connecting the results of Table III it was possible to estimate the amount of acid neutralised corresponding to the voltage readings of Table II. The dissociation constants were then calculated by means of the equations

$$\text{CON}_2\text{H}_4 + \text{H}^+ \rightleftharpoons \text{CON}_2\text{H}_5^+$$

$$K_{ab} = \frac{[\text{CON}_2\text{H}_5^+]}{[\text{H}^+] [\text{CON}_2\text{H}_4]}$$

$$\rho K_b = \rho K_w - \rho K_{ab}$$

TABLE III

Volume of 0.2 N NaOH Solt. Added.	Electrode Potential (millivolt).
2.4 c.c.	390.4
4.9 c.c.	380.2
9.9 c.c.	386.4
20.0 c.c.	370.2
25.0 c.c.	374.9

TABLE IV

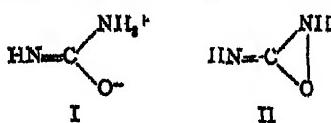
Solution.	Hydrolysis Constant (K_h).	Dissociation Constant (K_b).
I.	0.75	1.51×10^{-14}
II.	0.76	1.51×10^{-14}
III.	0.70	1.42×10^{-14}
IV.	0.78	1.44×10^{-14}
V.	0.75	1.49×10^{-14}

The value taken for K_b at 21° C. and ionic strength 0.1 was 1.744×10^{-14} (Harned and Hamer,³). At this temperature the average value of K_b was found to be 1.47×10^{-14} (Table IV).

Attempts to detect buffering by urea in alkaline solutions were made by a method similar to that used above except that the hydrogen electrode was used instead of the quinhydrone electrode. Every effort was made to exclude carbon dioxide. No buffering was detected.

Discussion.

Of the many formulae that have been suggested for urea the most interesting from the point of view of the dissociation constant is the cyclic formula of Werner.⁵ This formula as originally given by Werner includes a pentavalent nitrogen atom. It is now known from the electronic theory of valency that one of the five valencies of pentavalent nitrogen must be an electro-valency. Consequently Werner's formula should be written as a zwitterion I and not as II. The high dipole moment of urea in solution has recently been put forward by Bergmann and Weizmann⁴ as evidence in support of a zwitterion structure. If this is so, we should expect the



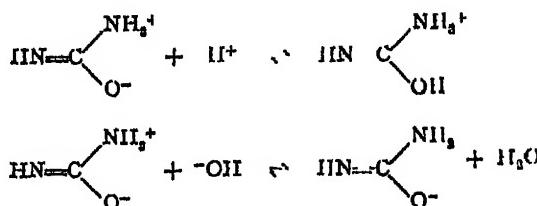
formula of Werner.⁵ This formula as originally given by Werner includes a pentavalent nitrogen atom. It is now known from the electronic theory of valency that one of the five valencies of pentavalent nitrogen must be an electro-valency. Consequently Werner's formula should be written as a zwitterion I and not as II. The high dipole moment of urea in solution has recently been put forward by Bergmann and Weizmann⁴ as evidence in support of a zwitterion structure. If this is so, we should expect the

³ Harned and Hamer, *J. Am. Chem. Soc.*, 1933, 55, 2194.

⁵ Werner, *The Chemistry of Urea*, 1923, Longmans, Green & Co.

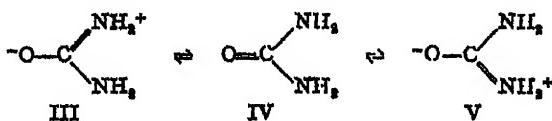
⁴ Bergmann and Weizmann, *Trans. Faraday Soc.*, 1938, 34, 783.

following reactions in acid and alkaline solutions, with consequent marked buffering in both:



The results reported by Walker and Wood and confirmed in this paper show that urea is certainly a very weak base, and that within the limits of experimental error it has no acidic properties even in strongly alkaline solutions. These findings constitute strong evidence that urea in solution is neither wholly nor in part zwitterionic. Moreover, Ebert^{5, 6} has contested the view that the presence of zwitterions is necessary to explain the dielectric properties of urea in solution. Furthermore, Kumler and Fohlen⁷ have recently remeasured the dipole moment of urea in dioxan, with the precautions necessary for this determination in the case of a weakly polar substance in dilute solution. The value obtained by them is approximately half that given by Bergmann and Weizmann. The view of Bergmann and Weizmann, therefore, rests on unsatisfactory ground.

Pauling, Brockway, and Beach⁸ have suggested that the urea molecule should be considered as a resonating hybrid of the structures



in which each of the forms has approximately equal importance. The forms III and V are identical, each having a separation of charges with no proton transfer.

Kumler and Fohlen⁷ on the basis of their measurements of the dipole moment point out that their results can be explained by assuming a 20% contribution from forms III and V together. Now if the true structure of urea is really a hybrid of forms III, IV, and V the $\text{C}(\text{NH}_3^+)$ end of the molecule will be the positive end of the dipole. This would oppose the union with the H^+ ion, and may be the explanation of the low values of K_b found.

The fact that urea is monobasic and not dibasic has been given as evidence by Werner against the carbamide structure. The value of the first dissociation constant is, however, so low that if a second existed it would be undetectable. Furthermore, the hydrolysis of salts of urea in aqueous solution is so great that double salts are not formed under conditions so far investigated.

Summary and Conclusions.

(1) The basic dissociation constant of urea has been re-measured and found to be $ca. 1.47 \times 10^{-14}$ at 21°C .

⁵ Ebert, *Z. physik. Chem.*, 1926, 122, 28.

⁶ Ebert, *Ber.*, 1931, 64, 679.

⁷ Kumler and Fohlen, *J. Am. Chem. Soc.*, 1942, 64, 1944.

⁸ Pauling, Brockway, and Beach, *ibid.*, 1935, 57, 2705.

(2) Attempts to measure the acidic dissociation constant support the view that while urea may be regarded as a weak base, it has no detectable amphoteric properties.

(3) The findings are considered to be contrary to the theory that urea in solution has a zwitterion structure.

(4) An attempt has been made to explain the monobasicity and the low value of the basic dissociation constant in terms of resonance theory.

The publication of this work has been delayed by the death of the senior author (J. B.). While his opinions on the present problem were along the lines expressed here, we unfortunately have not had the benefit of his expert help in forming the conclusions to this paper.

We wish to thank Professor A. J. Allmand, F.R.S., for his helpful criticism of this work.

A CHEMICAL INTERPRETATION OF THE MECHANISM OF OXIDATION BY DEHYDROGENASE ENZYMES.

By W. A. WATERS.

Received 29th January, 1943.

The fact that the vast majority of the well-defined reactions of living cells are brought about easily by enzyme catalysts, but only with very great difficulty, if at all, by the direct attack of simple chemical reagents is the distinguishing feature of biochemistry. So long as biochemical reactions are thought of as being peculiar catalytic processes, the theoretical outlooks of biochemists will remain aloof from those of synthetic organic chemists, but undoubtedly it should be possible to interpret the mechanisms of all chemical reactions on the basis of one consistent physical theory. With this object in mind, an attempt is made below to show that relatively simple physico-chemical mechanisms can be suggested for all those biochemical oxidations which are, as yet, only brought about by the catalytic action of dehydrogenating enzymes.

Chain Mechanisms for Enzyme Reactions.

Dehydrogenase systems, in general, act as follows : a simple chemical (the substrate) is dehydrogenated by the action of the enzymic catalyst, but the hydrogen thus abstracted passes to a Co-enzyme, or to an easily reducible substance, which may be oxygen, hydrogen peroxide, methylene blue, etc. The enzyme itself probably acts by way of a specific proximate group, and, in the vast majority of known cases, the catalytic activity of the enzyme is very gradually destroyed as the main catalysis proceeds.

To a physical chemist it is immediately apparent that this is a *chain reaction process* in which the enzyme is the chain initiator, and the substrate and co-enzyme the main reactants.^{1, 2} To give an example, one would write for the simple reaction :



¹ Compare Haber and Willstätter, *Ber.*, 1931, 64, 2844.

² Moelwyn-Hughes, *Ergebnisse der Enzymforschung*, 1937, 6, 25.

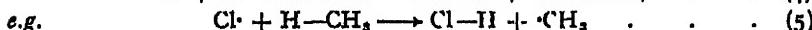
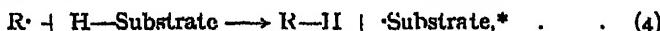
Na atom = Enzyme Prosthetic Group;

Cl₂ molecule = Co-enzyme : H, molecule - substrate, or the reverse, and numerous examples of gas reactions could be quoted to show how a chain process, when once initiated, can proceed so that molecules of many different types are involved.

These chain reactions, once started, proceed with great vigour because the transient active entities, though numerically few, are free atoms or neutral radicals, and not stable covalent molecules or ions. Though in general the reactions of simple organic molecules in solution do not involve the formation of free radicals, it is becoming recognised that many of the somewhat abnormal reactions of organic compounds in solution do involve free radical formation,³ and the kinetic characteristics of these reactions can be worked out along lines already explored for gaseous systems.⁴ In particular it now seems that many oxidation processes are of this free radical type.^{4, 5, 6, 7}

Dehydrogenase Action of Free Radicals.

There are strong theoretical reasons⁴ for believing that when a free radical attacks an organic molecule it reacts only with one of the outermost atoms, and since, in general, all organic molecules have hydrogen atoms on their periphery, it follows that the normal action is one of hydrogen abstraction.



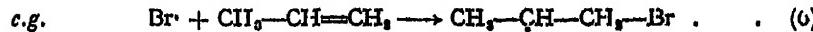
This is the essential primary step in an enzyme dehydrogenase process.

Since the bond energies of covalent hydrogen are nearly equal in all organic compounds (Pauling⁸ gives

Bond	C—H	N—H	O—H	S—H
Energy (k. cal.)	87·3	83·7	110·2	87·5

it follows that, once this primary dehydrogenation process has occurred, the resulting organic radical is capable of re-abstracting hydrogen from a second organic molecule (particularly from a C—H, N—H or S—H group, rather than from an O—H group) without receiving much more fresh activation energy than that kinetically available.

Whilst free radicals dehydrogenate saturated compounds, they can add on to olefinic groups, but again they produce thereby new free radicals capable of continuing the chain process,



The typical hydrogen acceptors of biochemical systems are, in fact, unsaturated compounds to which neutral radicals can be united, but from which, after complete or partial reduction, the attached groups can be split off with ease.

Thus a coenzyme which is reduced by one dehydrogenase process may be oxidised rapidly by another reaction occurring simultaneously in the same vicinity: e.g. (A—C) and (E—G) (below) may well be conjoint processes within a single living cell.

³ Hey and Waters, *Chemical Reviews*, 1937, 21, 169.

⁴ Waters, *Trans. Faraday Soc.*, 1941, 37, 770.

⁵ Waters, *J. Chem. Soc.*, 1939, 1805.

⁶ Farmer, Bloomfield, Sundralingam and Sutton, *Trans. Faraday Soc.*, 1942, 38, 348.

⁷ Farmer and Sundralingam, *J. Chem. Soc.*, 1942, 121.

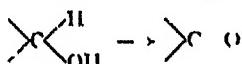
⁸ In all these equations a single dot is used to denote a single electron.

⁹ *The Nature of the Chemical Bond*, 1940.

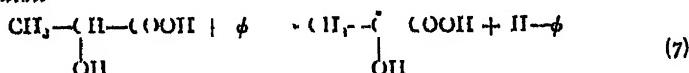
Typical Chain Mechanisms of Biochemical Oxidation.

Denoting the initiating radical of an enzyme by the symbol ϕ , one can formulate the mechanism of a number of enzyme processes as indicated below:

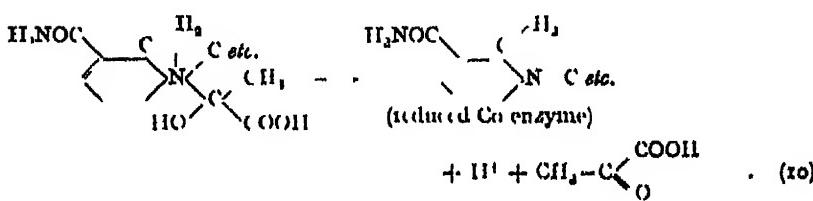
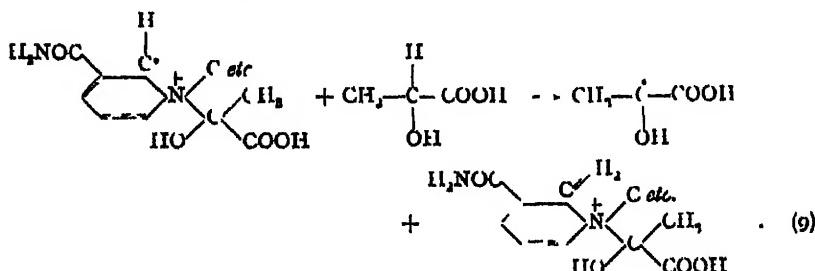
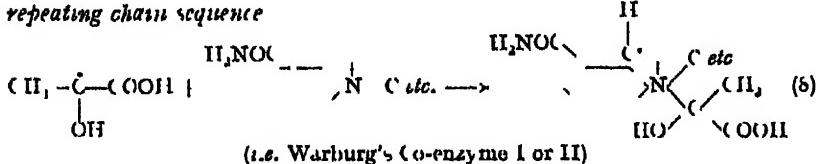
(A) Lactate Pyruvate, and similar systems, involving



chain initiation



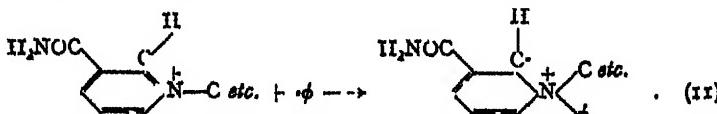
repeating chain sequence



compare $\text{CH}_3 \text{C}(\text{O}-\text{NH}_2)=\text{CH}_2 + \text{CH}_3\text{CHO} + \text{NH}_3$;

the splitting of an aldehyde-ammonia in water

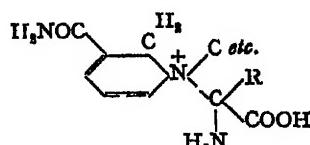
An alternative, and less probable formulation of the chain-initiation stage is to assume Enzyme + Co-enzyme union in the radical form;



followed by stage (9) above, and then by the repeating reaction series (8) to (10).

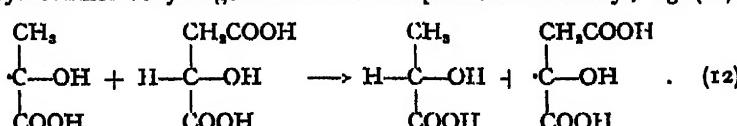
Action (11) is plausible only if ϕ is a tervalent carbon radical, $R\dot{C}^{\bullet}$, whereas reaction (7) can occur with *any* radical ϕ that can accept hydrogen.

All systems involving Co-enzymes I or II, and the $\begin{array}{c} \text{H} \\ | \\ \text{C} \\ | \\ \text{OH} \end{array}$ group can be expressed as above, and amino-acid oxidase systems can be written out similarly, for the group $\begin{array}{c} \text{H} \\ | \\ \text{C} \\ | \\ \text{NH}_2 \end{array}$ would give a complex



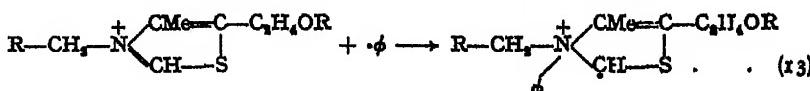
which would immediately be hydrolysed by water, *via* the unstable kation $\begin{array}{c} \text{R} \\ | \\ \text{C} \\ | \\ \text{NH}_2 \end{array}^+$, COOH , to a keto-acid and ammonia.

In a chain reaction such as this, any intermediate radical, if offered a choice of substrates, may dehydrogenate one compound preferentially. Co-enzyme linked dehydrogenations can be explained in this way; e.g. (12).

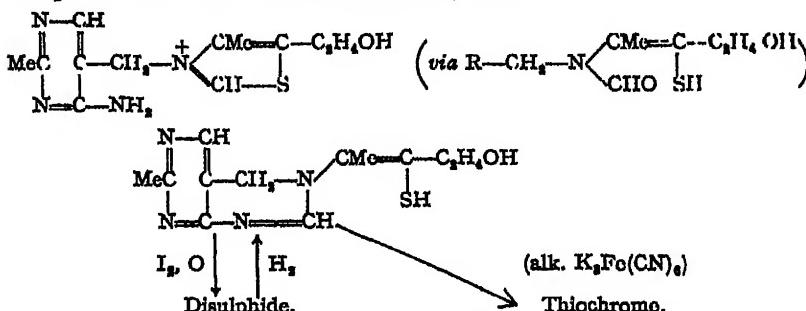


(B) Aneurin Dehydrogenases.

Vitamin B₁, and its related Co-enzymes, e.g. Co-carboxylase, could, like Warburg's Co-enzymes I and II, be reduced in stages by free radical addition, the first stage of which can be represented as (13).*

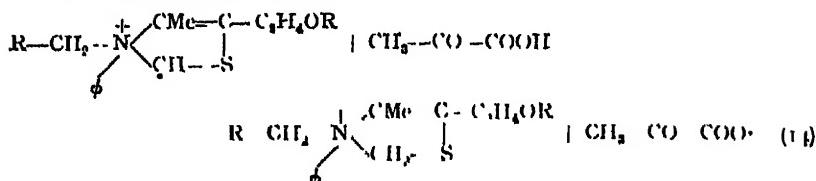


* The author's attention has been directed to recent papers by Zima and Williams (*Ber.*, 1940, 73, 941), Schöberl and Stock (*Ber.*, 1940, 73, 1240) and Zima, Ritsert and Moll (*Z. physiol. Chem.*, 1941, 267, 210), who consider that, at biological pH's, Vitamin B₁ acts as a thiol, capable of reversible oxidation to a disulphide rather than of further reduction; thus—

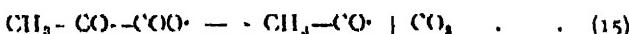


Hence it might be preferable to include reactions of aneurin and its related compounds amongst those of Section G (below, p. 149), with chemical changes of the types of equations (45) and (46) in place of equations (13), (14), and (20). However, Barron and Lyman (*J. Biol. Chem.*, 1941, 141, 951) have presented

Carboxylase action could then be represented as



followed by



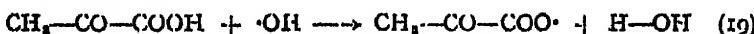
(compare benzoyl peroxide



and either (17) or (18),

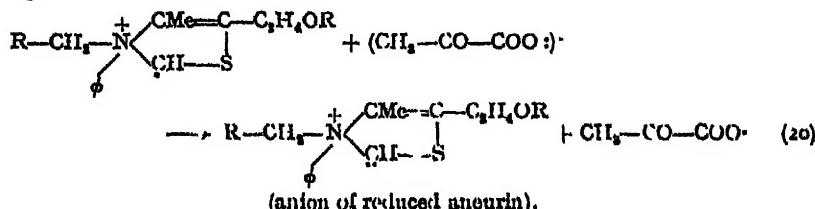


giving, in case (17), H^\cdot atoms which would be picked up by an acceptor like the co-enzyme, or methylene blue, or, in case (18) the $\cdot\text{OH}$ radical which would dehydrogenate more pyruvic acid and continue the chain process to stage (19),



or, alternatively oxidise the reduced aneurin to the radical, and thus continue a cycle including equation (14).

The $\text{CH}_3-\text{CO}-\text{COO}^\cdot$ radical, formulated first in equation (14) above could alternatively, and probably better, be thought of as a neutral product derived from the anion of pyruvic acid by abstraction of a single electron, e.g.

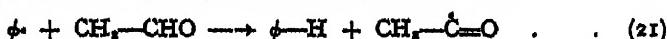


Any electron donor, such as the hydrogen atom produced in stage (17) above could, in this case, initiate the reduction cycle with aneurin (i.e. by equation (13) where $\cdot\phi = \cdot\text{H}$), and so there is no need to postulate extensive combination between an active enzyme and a co-enzyme of the aneurin type.

(C) Aldehyde Mutases.

e.g. $\text{CH}_3\text{CHO} + \text{CH}_3\text{CO}-\text{COOH} \rightarrow \text{CH}_3-\text{COOH} \cdot + \text{CH}_3-\text{CIOH}-\text{COOH}$.

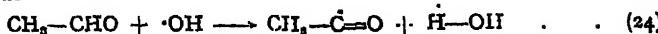
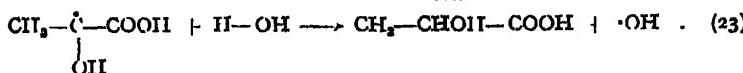
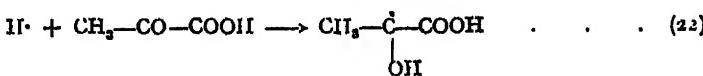
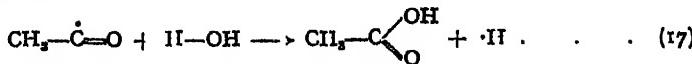
These are similar in type to the systems discussed above, for they are essentially Cannizzaro reactions, and involve actions such as



evidence to indicate that aneurin does not act as an oxidation-reduction system of the glutathione type, and consequently its precise mode of action must still be regarded as *sub judice*.

Since the rest of the reaction sequence would be the same in both cases, the development of the main hypothesis of this paper is not materially affected.

(ϕ being either the enzyme or the co-enzyme intermediate radical) followed by the sequence



where (24) is the reversible alternative to (18).

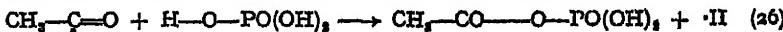
For a more elaborate treatment of this reaction, reference may be made to a recent paper by Weiss,⁸ and the following theoretical discussion.¹⁰

The greater energy required to break H—O linkages rather than H—C linkages is an argument against reactions (17) to (24) above in this simple form, though it may be pointed out that over 40 % of the energy of an ionisable H—O bond is ionic,⁹ and consequently dependent very much on the $p\text{H}$ of the environment. Nevertheless, reaction of the derived anions (compare equation (20)) is, under biological conditions, rather more likely throughout than reaction of the undissociated carboxylic acids.

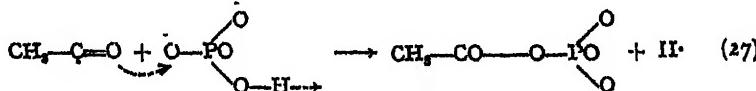
Moreover, in these stages of the chain process, *phosphorylation* is a likely alternative in a biochemical system. The observation that a surface film of phosphoric acid greatly prolongs the apparent life of atomic hydrogen¹¹ seems to indicate that the unionised H—OP link of phosphoric acid (or of NaH_2PO_4 or Na_2HPO_4) can be broken more easily than a water molecule by the interchange reaction (25).



(compare $\text{H}^* + \text{D}_2\text{O} \longrightarrow \text{HOD} + \cdot\text{D}$), and thus one would anticipate that the reaction (26) would be more facile than reaction (17).



An alternative representation of reaction (26), which is more particularly relevant to reactions in solutions of high $p\text{H}$, is (27), which takes account



of the fact that the exterior of the relatively large phosphate anion is chiefly composed of oxygen atoms, any one of which could unite to the active radical, thus increasing the probability of occurrence of radical interchange between the organic group and HPO_4^{2-} anions in comparison with interchange with water molecules.

Acyl phosphoric anhydrides, such as that formulated in equations (26) and (27) have actually been isolated from enzymatic pyruvate oxidations by Lipmann,^{12, 13} and are obvious reagents for the production of phosphato

⁸ Weiss, *Trans. Faraday Soc.*, 1947, 37, 783.

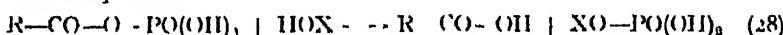
¹⁰ *Ibid.*, p. 792.

¹¹ Harteck, *Z. Elektrochem.*, 1936, 42, 536.

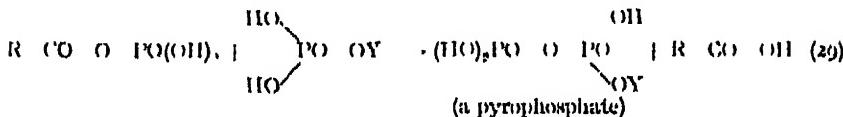
¹² Lipmann, *J. Biol. Chem.*, 1940, 134, 463.

¹³ Lipmann, *Nature*, 1939, 143, 436.

amides (e.g. phospho-creatine) or esters (e.g. equations (28), (29)) by biochemical processes.



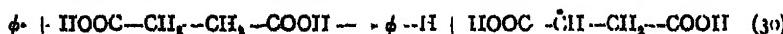
(where HOX may be, amongst other possibilities, a sugar or a phosphate).



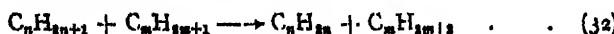
Kalekar,¹⁴ in a recent review of this subject, has commented in detail on the biochemical significance of the energy changes in biochemical oxidations from the aspect of whether or not phosphorylations are involved. The acceleration of particular enzyme oxidations by addition of phosphate can obviously be interpreted along the lines suggested above, with the successive reactions (26, 27) and (28, 29) replacing the reaction (18), and consequently altering the relative probability of occurrence of the alternative reaction processes (17) and (18).

(D) Succinic Dehydrogenase.

The reduction of succinic acid to fumaric acid can easily be represented as a disproportionation of the radical left after one hydrogen atom has been abstracted from a succinate:



and thus may be a biochemical instance of the formation of an olefine by the action of a free radical on a paraffin chain,



comparable exactly with the results obtained by Bamford and Norrish,^{15, 16, 17} in their studies of the photolysis of aldehydes and ketones in paraffin solution, and with modern views of the mechanism of "cracking" of gaseous hydrocarbons.

Reaction Promoters in Enzymes.

So far in this paper the chemical nature of the active radical, ϕ , of the enzyme catalyst has not received consideration. As will be shown below, there are numerous possibilities. Some of these groups may have energy enough to remove hydrogen from H---C in CH₃, others from H---C in CH(OH) or CH(NH₂) or CH=O, and others from O---H of COOH or H₂PO₄, and since bond energy differences of very few (1-5) kilocalories correspond to differences of several hundred-fold in reaction rates of free radicals, it is not surprising that enzyme catalysts are highly specific with regard to the type of reaction which they can initiate. Moreover, the activation energy of reactions involving the abstraction of hydrogen, or an electron, from ---COOH, or addition of a radical to tertiary or quaternary nitrogen (e.g. nicotinic acid or aneurin) is dependent upon the *pH* of the exact environment, which is, as a rule, the surface of the enzyme--co-enzyme colloid on which the *d* and *l* forms of even a simple optically active substrate such

¹⁴ Kalekar, *Chemical Reviews*, 1941, 28, 77-178.

¹⁵ Bamford and Norrish, *Nature*, 1936, 138, 1076; 1937, 140, 105.

¹⁶ Bamford and Norrish, *Trans. Faraday Soc.*, 1937, 33, 1522.

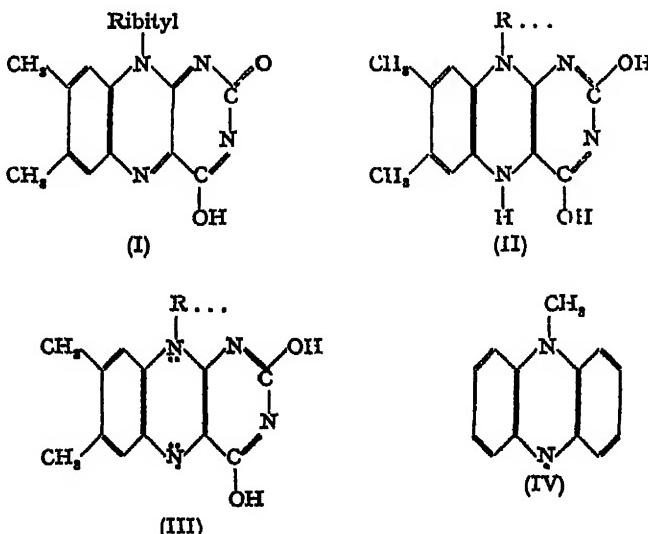
¹⁷ Bamford and Norrish, *J. Chem. Soc.*, 1938, 1531, 1544.

as malic acid will be differently absorbed, since salts of optically active acids with protein bases are not enantiomorphs.

Bearing in mind the possibility of amplifying the general conception of free radical promoter action of enzymes by the above considerations, one can indicate below some potential chain initiators that do occur in known enzymes.

(E) Flavoproteins, Pyocyanine and Allied Pigments.

Riboflavin (I) reduces in two stages to leucoflavin (II), and, as Michaelis has shown,^{18, 19, 20} intermediate quinhydrone complexes can, and frequently do, dissociate into free radicals which one can write as (III). In the case of both riboflavin itself,²¹ and the bacterial pigment pyocyanine,^{22, 23} there is definite magnetic evidence for the existence of the reduced free radical intermediates (III) and (IV).



Chemically, these radicals resemble triphenylmethyl and its analogues, which are well known as oxygen carriers for the oxidation of aldehydes and olefines,²⁴ and amongst which rubrene is strikingly like haemoglobin in catalytic activity.²⁵ Still more closely analogous is the radical formed by thermal dissociation of tetraphenyl-hydrazine.²⁶



The reactions of these biochemically-occurring phenazyl and *iso*-alloxazyl radicals can be two-fold :

¹⁸ Michaelis, *J. Biol. Chem.*, 1936, 116, 587.

¹⁹ Michaelis, *Chemical Reviews*, 1935, 10, 243; 1938, 20, 437.

²⁰ Michaelis, *J.A.C.S.*, 1938, 60, 1678.

²¹ Kuhn and Strobel, *Ber.*, 1937, 70, 753.

²² Kuhn and Schön, *ibid.*, 1935, 68, 1537.

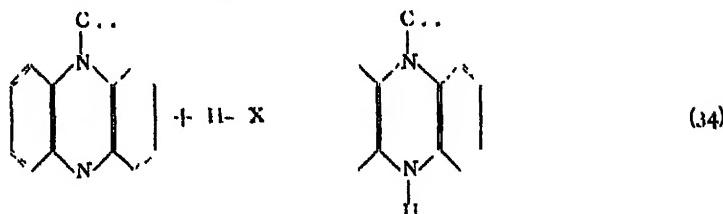
²³ McIlwain, *J. Chem. Soc.*, 1937, 1706.

²⁴ (a) Zeigler and Ewald, *Annalen*, 1933, 504, 162; (b) Zeigler and Gänicke, *Annalen*, 1942, 551, 213.

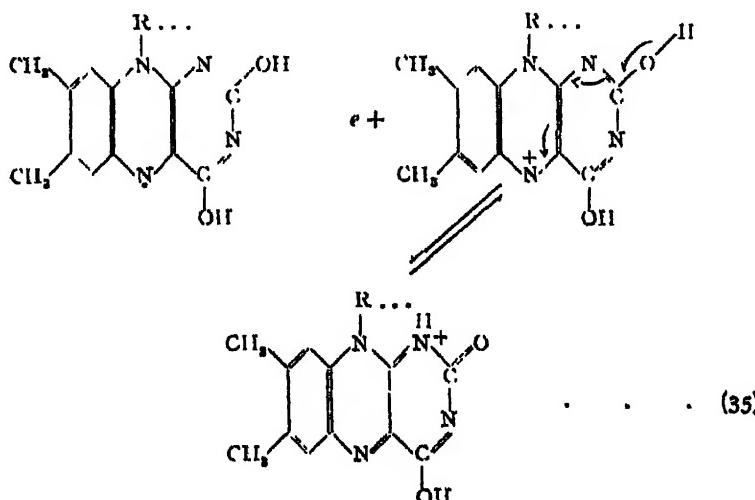
²⁵ Schumacher, *Z. Electrochem.*, 1936, 42, 522 (and earlier papers by Dufraisse).

²⁶ Wieland, *ibid.*, 1911, 381, 206.

(a) Further reduction; *i.e.* combining with hydrogen, taking up thereby *one* electron, *e.g.* (34).



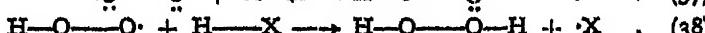
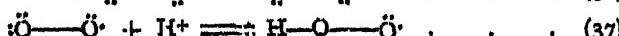
(b) Loss of *one* electron to give the cation of the flavine or phenazine in its oxidised form:



Reactions of type (a) have been discussed in the preceding part of this paper.

Reactions of type (b) will explain the autoxidation of leucosflavin and of phenazins by processes already established by kinetic studies in the triphenylmethyl series,^{24, 25} and the formation of hydrogen peroxide thereby.

Thus the reduction of gaseous oxygen is most simply represented by the following series of chain processes (36-38) which resemble the scheme used for interpreting the mechanism of the hydrogen-oxygen gas reaction when initiated by atomic hydrogen.^{21, 22, 23}



In biochemical systems X· of equation (38) can be a radical concerned in a substrate + co-enzyme chain oxidation, and H-X a reduced co-enzyme or substrate (including, of course, a molecule such as riboflavin).

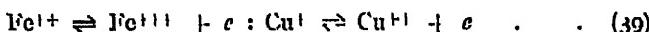
²¹ Taylor and Marshall, *J.A.C.S.*, 1926, **48**, 2840; 1927, **49**, 2763.

²² Taylor and Marshall, *J. Physic. Chem.*, 1925, **29**, 1140.

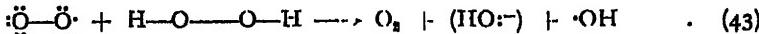
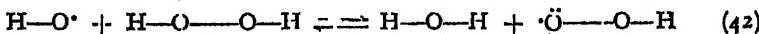
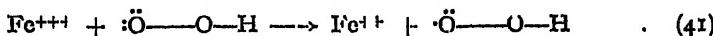
²³ Geib and Hartbeck, *Ber.*, 1932, **65**, 1551.

(F) Iron and Copper Porphyrins (including Cytochrome).

Iron and copper (and possibly manganese) compounds can undergo one-electron transitions at specific oxidation-reduction potentials, which depend very much upon the precise mode of linkage of the metal to the other groups.

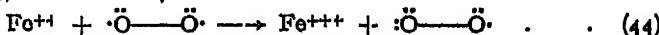


According to Pauling,²⁰ some of the iron-porphyrin complexes contain unpaired electrons, and are structurally unlike the more stable ferro- and ferri-cyanides, or the complex ferri-fluorides. Haber and Willstätter in 1931,²¹ and later Haber and Weiss,²² and Weiss²³ have indicated how these single-electron transfers could operate in enzymatic processes, with particular reference to catalase and peroxidase. The essential reactions postulated are



which are concordant with kinetic evidence adduced from the study of the decomposition of hydrogen peroxide in the presence of iron salts. Weiss suggests that catalase acts mainly in the ferrous form and peroxidase mainly in the ferric form, and this will provide an explanation of the difference between peroxidase action and oxidation by means of Fenton's reagent,²⁴ for in the latter system a ferrous salt is the active catalyst.

The biochemical role of the $\cdot\text{OH}$ radical has been indicated in the sections dealing with co-enzymes, and the role of the $\text{H}-\text{O}^\bullet-\text{O}$ radical in the immediately preceding section (equation (38)). Both radicals are essentially electron acceptors which could play the part of the hypothetical radical ϕ^\bullet introduced earlier in this paper. It is known that the porphyrin enzymes, and analogous oxidation-chain carriers such as cytochrome, exist chiefly in the more oxidised (ferric or cupric) state, and one must therefore suppose that reaction (40) of the peroxidase system, leading to the destruction of hydrogen peroxide, occurs very readily in those systems which are not autoxidisable (e.g. Cytochrome-*c*), and reactions of the type of (44) (compare (36))



in those which are autoxidisable (e.g. Cytochrome oxidase).

The cyclic electron transfers envisaged above are similar to those postulated by the author for the interpretation of the Sandmeyer reaction,²⁴ and the same general stipulations with regard to the specificity of oxidation-reduction potentials are equally cogent for enzyme systems.

(G) Thiols and Disulphides.

There is a considerable amount of evidence to support the view that organic disulphides can dissociate into free radicals on heating, and it is known that substances such as cystine are unstable in alkaline solution, and then prone to atmospheric oxidation. In view of the structural similarity between the disulphides and the peroxides, it is not unlikely that

²⁰ Pauling, *The Nature of the Chemical Bond*, 1940, pp. 115-17.

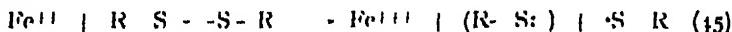
²¹ Haber and Weiss, *Proc. Roy. Soc. A*, 1934, 147, 332.

²² Weiss, *J. Physic. Chem.*, 1937, 41, 1107.

²³ Mann and Saunders, *Proc. Roy. Soc. B*, 1949, 119, 47.

²⁴ Waters, *J. Chem. Soc.*, 1942, 266.

iron-protein compounds could give rise to thiol radicals, which would be hydrogen acceptors.

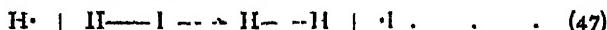


Consequently disulphides and thiols could, by conversion into intermediate neutral thiol radicals, $\text{R-S}\cdot$, be chain carriers in dehydrogenase processes. In confirmation of this, Ziegler and Gämmeke²⁶ have demonstrated recently that thiophenol is a powerful catalyst of autoxidation. Since, however, the bond energy of the S-S link is rather high (6.4 k. cal.), it is more likely that the formation of the thiol radicals $\text{R-S}\cdot$ is a secondary (co-enzymic) process than a primary activation process, and this is in accord with the known behaviour of glutathione.

Inhibition of Enzyme Systems.

It is a characteristic feature of enzyme catalysis that traces of compounds, such as potassium cyanide, sodium fluoride, carbon monoxide or sodium iodoacetate, have specific inhibiting properties on particular enzymes.

No less striking is the ease of inhibition of gaseous chain-reactions by traces of substances, such as nitric oxide, propylene or hydrogen iodide, which act either by combining with free radicals to give stable compounds, or by exchange reactions with active radicals, forming thereby radicals, such as atomic iodine, which have too little intrinsic energy to attack the covalent bonds of other molecules (e.g. (47))



(whereafter $\cdot\text{I}$ can only react by self-combination, since it has too little available energy to disrupt an H-X link).

The comparison between these two groups of negative catalysts affords further confirmation of the hypothesis of free radical action in enzyme systems, for the inhibitors of enzyme processes are concordantly inhibitors of atomic chain processes.

Thus (a) groups like $-\text{CN}$, $-\text{F}$, CO , NO form with ferrous and ferric salts stable co-ordinated complexes in which unpaired electron structures are no longer present.²⁵ Oxidation-reduction by single electron transfer then becomes impossible.

(b) Molecules like iodoacetic acid may react with free organic radicals to give relatively inert products with which the chain processes cannot be continued.



A more detailed discussion of the effect of substituent groups on the ease of free radical formation from derivatives of iodoacetic acid, malonic acid, etc., has already been given by the author.^{25, 26} In general, the more easy the fission of a covalent bond to neutral radicals the less reactive chemically will be the resulting fragments. Once there is formed a neutral radical which has not sufficient intrinsic energy to disrupt a H-C bond then there is terminated abruptly a dehydrogenase chain-reaction sequence.

(c) Complex organic free radicals, such as the phenazyls (pyocyanoine, etc.) can be stabilised by reaction with cyanides, sulphites, etc., as McIlwain has shown.²⁷ Again, one can suppose that the available energy of the radical has been lowered below a certain critical value.

Thus the common tests by which biochemists differentiate between various enzyme systems are none other than reactions by which specific active free radicals are irreversibly destroyed.

²⁵ Waters, *J. Chem. Soc.*, 1942, 153.

²⁶ *Ibid.*, 1933, 1551.

Summary.

1. General analogies between biochemical oxidations catalysed by dehydrogenases and free-radical chain oxidations are pointed out, and special emphasis is given to the fact that free radicals regularly dehydrogenate aliphatic molecules.

2. An enzyme catalyst is regarded as a supplier of an active free radical, whereby a chain reaction involving a substrate and a co-enzyme, and ultimately oxygen or an oxidising agent, is set up. This scheme is applied to several dehydrogenase systems, and the special rôle of phosphates in enzyme reactions receives comment.

3. It is pointed out that many known enzymes can either give free radicals by dissociation of prosthetic groups (*e.g.* flavoproteins), or else can initiate single-electron oxidations and reductions (*e.g.* iron-porphyrins).

4. The inhibition of specific enzymes by substances such as potassium cyanide or sodium iodoacetate is explicable as a destruction of free radicals, or as a replacement of active radicals by others too inert to perpetuate the reaction chain.

Acknowledgments.

The author recognises that the general theory of dehydrogenase action which has been set forth above is a speculative conception, dependent upon the application of our present scanty knowledge of free-radical reactions in solutions to exceedingly complex systems, of which the fundamental reactions are as yet known only in outline. It would appear, however, that there now awaits development a wide field of experimental research in investigating the actions of known free radicals on simple biochemical products, and it is hoped that this paper may serve a useful purpose in drawing attention now to the significance of this subject, which the author is, at present, unable to study experimentally.

He wishes to express his thanks to Professor R. A. Peters, and to Mr. K. P. Harrison for their valuable criticisms and helpful suggestions.

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ON THE THEORY OF THE PERIODIC STRUCTURE OF PROTEINS.

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Bergmann and Niemann,¹ on the basis of their own work on the analysis of the constituent aminoacids of proteins, and that of earlier workers, put forward these hypotheses :—

- (1) that the numbers of molecules of different aminoacids occurring in a protein are in simple ratios, such that the numbers can be expressed as $2^m 3^n$, where m , n are small integers.
- (2) that the total number of aminoacid radicles of all sorts in the smallest analytical unit (minimum molecular weight) of a protein is of the form $2^m 3^n$, and therefore that the reciprocal of the fraction of radicles contributed by any one aminoacid is of the form $2^m 3^n$.
- (3) that the radicles of each sort of aminoacid occur at regular intervals in the peptide chain of which the protein essentially consists, the intervals being of the form $2^m 3^n$ places.

¹ Bergmann and Niemann, *J. Biol. Chem.*, 1937, 118, 301; 1938, 122, 577. Bergmann, *Chem. Rev.*, 1938, 28, 423.

Neuberger² and Pirie³ criticised these hypotheses on the ground that the accuracy of the available analytical figures was insufficient to justify them. Chibnall⁴ has recently contributed a discussion together with new analytical data of much greater accuracy; he suggests that the data for celestin and insulin are consistent with the above hypotheses while those for β globulin of milk and egg albumin are not, possibly because the latter are composed of several non-identical sub-units.

The accuracy of the experimental data required to establish the three hypotheses differs. Where (as in most of the proteins which have been examined) the molecular weight is known approximately, the error permissible in the analysis in order to establish the number of radicles of an aminoacid in the analytical unit is inversely proportional to that number; thus less accuracy is needed to show that there are 3 rather than 4 or 2 radicles of cysteine in a molecule of cattle globin than to show that there are 32 rather than 33 or 31 radicles of α -partic acid. Accuracy of the order required to establish the numbers of even the most abundant aminoacids seems to be within reach; it should therefore be possible to prove or disprove the first hypothesis.

The second hypothesis is not a necessary consequence of the first unless the third also is true, since any number can be formed by the sum of numbers of the form $2^n \cdot 3^m$. To establish the second it is necessary to know the total number of radicles in a molecule or analytical unit; for example, to show that there are 288 rather than 289 or 287 radicles in a unit of cattle globin. Accuracy of this order does not at present seem attainable even with Chibnall's improved method of estimating the average radicle weight.

If the third hypothesis were true as well as the first, the second is proved since the total number of radicles must then be the lowest common multiple of the reciprocals of the fractions of molecules contributed by the various aminoacids. But the third is not a necessary consequence of the first and second, since shuffling any regular arrangement would destroy its regularity without affecting the relative or absolute numbers of amino-acid radicles. If the second is untrue, so also is the third.

There is satisfactory direct evidence for the third hypothesis only in the case of the protamine clupein.⁵ Bergmann and Niemann appear to have assumed unconsciously regularity of structure in asserting the proof of the second hypothesis. Chibnall and Gordon, Martin and Syngle⁶ point out that only the isolation of fragments of a protein can provide positive evidence of regularity of structure.

There is, therefore, little to support the hypothesis of regularity, and it must not be accepted merely because it is attractive. Nevertheless, it seemed to be worth while to find what limitations would be imposed by regularity on the structure of proteins. This problem does not seem to have received much attention; Niemann⁷ has made some contributions; Bull⁸ points out that two mutually prime intervals cannot co-exist in a regular structure, but his statement about the number of exact divisors of 288 is untrue. The mathematical theory of Congruence deals with the converse of the present problem which may therefore be termed the study of Incongruence.

² Neuberger, *Proc. Roy. Soc. B*, 1939, 127, 25.

³ Pirie, *Ann. Rep. Chem. Soc.*, 1939, 36, 352.

⁴ Chibnall, *Proc. Roy. Soc. B*, 1942, 131, 136.

⁵ Waldschmidt-Leitz, *Sitzungsber. Akad. Wiss.*, IIIb, 1935, 144, 489.

⁶ Gordon, Martin and Syngle, *Biochem. J.*, 1941, 35, 1369.

⁷ Niemann, *Cold Spring Harbor Symposia*, 1938, 6, 58.

⁸ Bull, *Advances in Enzymology*, 1941, I, 1.

Notation and Statement.

A polypeptide chain is regarded as an "array" of "places" to be filled by units (various aminoacids). Each sort of unit occurs in the array at regular intervals. The places in the array are numbered successively 1, 2, . . . from one end (from any selected place in a cyclic array). The "interval" is the numerical difference between two successive occurrences of a sort of unit (this term is preferable to "frequency" used by Bergmann and Niemann).

A set of places occurring at regular intervals in the array is called a "sub-array"; a set of units occupying a set of places occurring at regular intervals is called a "series." A set of places occurring at regular intervals within a sub-array is called a "sub-sub-array," and so on, the index denoting the number of times that successive subdivision of the array is regarded as having been performed.

The starting points of series or sub-arrays (their least residues in the terminology of the theory of congruence) are denoted by x, y, \dots ; their intervals by P, Q, \dots ; A, B, \dots are factors of P, Q, \dots ; a, b, \dots are prime factors, α, β, \dots being the powers to which they occur in P, Q, \dots ; the highest common factor of two or more of P, Q, \dots is denoted by π .

The two necessary conditions that must be satisfied by a regular array are—

- (1) that no two series are congruent, that is, that units from no two series are required to occupy the same place in the array;
- (2) that all places in the array are occupied.

Condition (1). Incongruence.

Let any two series of interval P, Q start at x, y ; then for incongruence

$$x + mP \neq y + nQ,$$

where m, n are any positive integers; that is

$$mP - nQ \neq y - x \quad \dots \quad \dots \quad \dots \quad \dots \quad (1)$$

If P, Q are prime to each other, values of m, n can be found to give an equality in (1) for any value of $y - x$. But if

$$P = \pi A \text{ and } Q = \pi B$$

then (1) becomes

$$mA - nB \neq \frac{y - x}{\pi} \quad \dots \quad \dots \quad \dots \quad \dots \quad (2)$$

where A, B, \dots are prime to each other; no values of m, n make this an equality unless $y - x$ is an integral multiple of π .

Therefore the conditions of incongruence between any two series are that their intervals have a factor π (greater than 1) in common, and that they do not start a multiple of π places apart.

It follows that the largest number of incongruent series $\pi A, \pi B, \dots$ in an array, where A, B, \dots are all prime to each other, is π . For if π series of interval $\pi A, \pi B, \dots$ start in places $1, \dots, \pi$ in any order, all these are incongruent; let one of these of interval πK start at $x < \pi$ and another series (in addition to the above) of interval $\pi K'$ start in place $x + q\pi$ (where q is a positive integer) and let K, K' be prime to each other; then the condition of incongruence

$$x + m\pi K \neq x + q\pi + n\pi K'$$

or

$$mK - nK' \neq q$$

is not fulfilled. Therefore a series in addition to the first π series cannot start $q\pi$ places from a series with which it has only π as a common factor; that is, anywhere in the array, since all the first π places are already filled;

but the interval of any additional series must have at least a factor greater than 1 in common with the interval of each other series. In general, the interval of an additional series must be an integral multiple of the interval of that one of the first π series which starts $q\pi$ places from its starting place.

Condition (2). All Places in the Array are to be occupied.

Consider again π series of interval $\pi\Lambda, \pi B, \dots$, starting in place, 1, ..., π in any order. What further series must be added in order to fill the array without congruence? In the simplest type, each additional series must be of interval which is an integral multiple of the interval of that one of the above series starting $q\pi$ places from its starting point. The simplest method, then, of completing the filling is by repetition, that is, by using m_A series of interval $\pi\Lambda, m_B$ of interval πB , etc. Then

$$m_A/\pi\Lambda + m_B/\pi B + \dots = 1 \quad . \quad . \quad . \quad (3)$$

$$\text{whence} \quad m_A/\pi\Lambda = A \sum_{B, \dots} m_B/B = 1 \quad . \quad . \quad . \quad (4)$$

All the terms in (4) are integers; therefore $\sum m_B/B$ must either contain Λ as a factor in its denominator or be an integer; but since Λ is prime to each of B, \dots , it is prime to their product; therefore $\sum m_B/B$ is an integer. Therefore m_A/Λ is an integer, and the same is true of m_B/B , etc. Let $m_A = \mu_A \cdot \Lambda$, etc.; then (3) becomes

$$\sum_{A, \dots} \mu_A = \pi,$$

but μ_A, \dots are positive integers, and there are π of them. Therefore

$$\frac{\mu_A}{m_A} = \frac{\mu_B}{m_B} = \dots = \frac{1}{A, m_B, B, \dots}$$

This gives the basic filling from which the general pattern of the array is derived, including more complex arrangements.

Structure of an Array: Subdivision.

In the arrangement discussed, K series, each of interval πK , start at places $x, x + \pi, x + 2\pi, \dots$; between them they occupy all the places, $x + m\pi$ in the array, that is, all the places which would be occupied by a single series of interval π starting at x . The same is true for each of the other sets of series. This particular array has, in fact, been arrived at by subdividing it into π overlapping sub-arrays; the conditions for incongruence and complete filling in each sub-array are the same as in the array, in general in a subⁿ array. Thus, in the example given, the π sub arrays are further subdivided into Λ, B, \dots subⁿ-arrays respectively; by successive subdivision of any or all of these, new intervals may be introduced and the complexity of the array increased indefinitely.

Whenever subdivision is performed by a factor such as to raise the highest occurring power of any prime factor in the array, the size of the array, which is the lowest common multiple of all the intervals that it contains, is increased. Each successive subdivision need not be by a new prime and need not increase the highest occurring power of a prime; in such cases the order of successive subdivision is not unique, but the same set of series is obtained by any sequence of subdivision.

A final subdivision gives a number of sub-series of the same interval; this number is equal to the factor by which the final subdivision is performed.

The analysis of the structure of an array can be most simply done by a diagrammatic method which will be illustrated later.

More Complex Arrangements.

So far only those arrangements have been considered in which the interval of all series or subⁿ-arrays have one factor in common. It is possible for an interval to occur in the array which lacks a factor in common with *all* the rest, provided that it has a factor greater than 1 in common with the interval of each other series. The mode of occurrence of such an interval is much more restricted than of those obtained by successive subdivision. A general solution of arrays containing such intervals has not been obtained, but the following is a line of approach sufficient for the present purpose.

Consider an array containing series of intervals $\pi a, \pi b, \dots$, where a, b, \dots are prime numbers, and also containing one or more series of interval $\pi abc \dots$; this satisfies the minimum conditions. The array can be entirely filled with series of intervals $\pi a, \pi b, \dots$ by successive subdivision; some of these must be omitted or converted to admit the series of interval $\pi abc \dots$. Any series $\pi abc \dots$ may be regarded as the sum of π series each of interval $\pi abc \dots$ which start in places $x + mabc \dots$. Since π is prime to $abc \dots$, those places will occur once in each of the π sub-arrays of the array, in an order that depends on the order of places in which the sub-arrays start, before there is a recurrence in the sub-array in which the first of the places occurs. (This is identical with the sequence of least differences in the theory of Congruence.) Therefore, to accommodate the series of interval $\pi abc \dots$, at least one of each of the series $\pi a, \pi b, \dots$ must be omitted and the subⁿ-array which each occupied be subdivided by $b c \dots, a c \dots, \text{etc.}$, respectively.

Subdivision of one of each of the subⁿ-arrays permits the insertion of only one series $\pi abc \dots$; for suppose that such a series occurs at place p in the subⁿ-array derived from a πa series, and that its next occurrence is at q in the subⁿ-array derived from a πk series; then, if the subⁿ-arrays a and k start in places x, y ,

$$q - p = abc \dots = \pi \pi + y - x.$$

Thus is obtained a set of $\pi - 1$ independent equations containing, in pairs, the π places of occurrence of the series $\pi abc \dots$ and there is only one solution of these such that all the places of occurrence are less than $\pi abc \dots$, that is, are contained in the array; this set of places repeats with each repetition of the $\pi abc \dots$ array. The places of occurrence of the $\pi abc \dots$ series in the array is therefore uniquely determined by the values of a, b, \dots and the starting places of the subⁿ-arrays chosen for subdivision.

Permutations of an Array.

The structure of the array is undisturbed by taking any number of places from the beginning and putting them in the same order on the end; identically, by closing the ends to form a cyclic array which may be re-broken at any point. Any subⁿ-array is interchangeable as a whole with any other of the same interval. Thus if successive subdivision is by a, b, c, \dots , by a', b', c', \dots , etc., and no combination of prime divisors is repeated except at the final subdivision, the number of arrangements of an open array is

$$\pi! \times \prod_a a! \times \prod_{a'} a'! \times \dots$$

Further arrangements become possible where the same combination of prime divisors occurs in two different subⁿ-arrays. The number is restricted by the combination of subⁿ-arrays to give an interval not having π as a factor.

Limited Arrays.

The units of the structures of some proteins contain of the order of 300 aminoacid radicles, or less. Where the size of the array is limited, the magnitude, number and powers of the primes that make up its intervals are limited, and therefore the degree of subdivision possible.

If the size of the array is $m^a b^b c^c \dots$, the number of different intervals which can occur is the number of exact divisors of the array which contain π as a factor, which is given by $\pi - \prod_{a_i} (\alpha_i + 1)$. The highest power of

each of a, b, \dots must occur in at least one interval of the array, either together or separately. The smallest number of series needed to fill the array is obtained by using π , and then a, b, \dots (in any order), to subdivide successively in each case *one* of the previously obtained sub-arrays; this number is

$$\pi - \sum_{a_i} \alpha(a_i - 1).$$

For an array of given size this number is smaller as -

- (1) π is smaller,
- (2) a, b, \dots are smaller, therefore $\alpha, \beta \dots$ larger.

TABLE I.

I. Numbers.	II. Factors.	III. Smallest Number of Series.	IV. Number of Divisors, with 1 Common Prime.
204	$2^2 \times 3 \times 17$	21	8, 6, 6
210	$2 \times 3 \times 5 \times 7$	14	8
216	$2^5 \times 3^2$	10	12
220	$2^2 \times 5 \times 11$	17	8, 6, 6
221	13×17	20	2
240	$2^4 \times 3 \times 5$	11	16, 10, 10
243	3^5	11	5
255	$3 \times 5 \times 17$	23	4
256	2^8	9	8
260	$2^3 \times 5 \times 13$	19	8, 6, 6
264	$2^5 \times 3 \times 11$	16	12, 8, 8
273	$2^4 \times 17$	21	8, 5
280	$2^3 \times 5 \times 7$	14	12, 8, 8
288	$2^5 \times 3^2$	10	15, 12
290	17^2	33	2
304	$2^4 \times 19$	23	8, 5
306	$2 \times 3^4 \times 17$	22	6, 8, 6
308	$2^2 \times 7 \times 11$	19	8, 6, 6
312	$2^3 \times 3 \times 13$	18	12, 8, 8
336	$2^4 \times 3 \times 7$	13	16, 10, 10
330	$2 \times 3 \times 5 \times 11$	18	8
340	$2^5 \times 5 \times 17$	23	8, 6, 6
352	$2^5 \times 11$	16	10, 6
357	$3 \times 7 \times 17$	25	4
360	$2^3 \times 3^2 \times 5$	12	18, 10, 12
364	$2^5 \times 7 \times 13$	21	8, 6, 6
374	$2 \times 11 \times 17$	28	4
385	$5 \times 7 \times 11$	27	4
390	$2 \times 3 \times 5 \times 13$	20	8
396	$2^5 \times 3^2 \times 11$	17	12, 12, 9

In Table I are given in column I selected numbers of the order of 300; column II their factors; column III the smallest number of series needed to fill an array of these sizes; column IV the number of divisors, having one prime in common.

Inspection of the table shows -

(1) That, if it be assumed that a maximum of 26 aminoacids are available, and that each occupies only one series, 10 is the largest prime that can occur in an array of this order of size.

(2) Low primes, such as 2 and 3, have no special suitability, though their use allows the construction of the greatest number of different sizes of arrays between given limits, the number of primes allowed being limited, and of the largest arrays using a

given number of series. Using only 2, and 26 aminoacids each occupying

only one series, the largest possible array is given by

$$2 + \alpha(2 - 1) = 26$$

whence the size of the array is 2^{26} .

On the other hand, the largest number of permutations of an array of given size is obtained by using the largest primes.

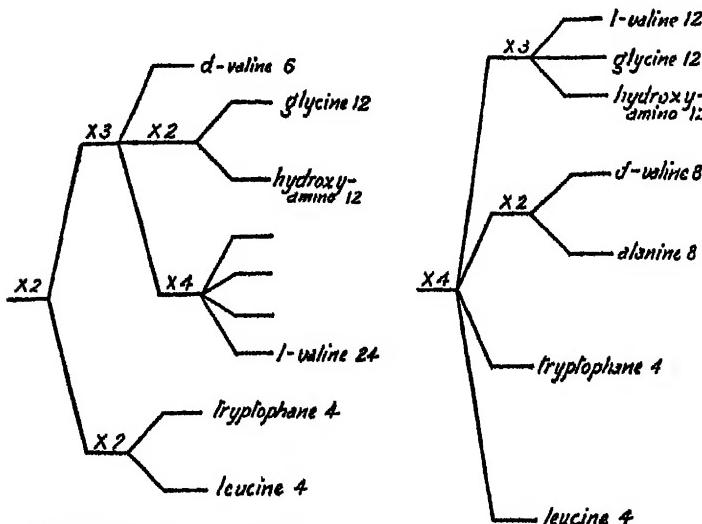
Applications.

(1) If any two intervals calculated from the analysis of a protein have not a factor greater than 1 in common, the protein cannot be in the form of a regular array. Thus in Bergmann and Stein's ⁸ values for gelatin the intervals 5 and 7 appear, and this at once excludes regularity. The same is true for the figures given by Chibnall ⁴ for edestin; arginine is given an interval of 9, and asparagine an interval of 16. Incidentally, the distribution of ammonia between glutamic and aspartic acids given by Chibnall is not unique in making the number of residues of these and their amides all of the form $2^m 3^n$, since the distribution, Table II, also satisfies this criterion.

But this, too, is inconsistent with regularity since the intervals of glutamine and arginine have no factor in common.

TABLE II.

	Interval.	Number.
Glutamic acid	24	18
Glutamine	8	54
Aspartic acid :	12	36
Asparagine :	48	9



No place for alanine 8. incomplete.

Complete.

Tree-diagrams of grammicidin. Numbers indicate subdivision and intervals.

(2) For a full test of regularity, complete analytical figures are necessary. The test is then simply performed by means of a tree-diagram; each successive subdivision is represented by a corresponding branching; the first subdivision is by the highest factor common to all series and the subsequent order is immaterial; each terminal branch must represent an

⁸ Bergmann and Stein, *J. Biol. Chem.*, 1939, 128, 217.

interval and all terminal branches must be occupied. The method is illustrated in the figure by application to Gordon, Martin and Syngle's recent data for gramicidin.¹⁰

TABLE III.

	Number.	Interval.
d-Leucine	6	1
Tryptophane	6	4
Alanine	3	8
Glycine	2	12
Hydroxyamino	2	12
L-Valine	1 or 2	24 or 12
d-Valine	4 or 3	6 or 8

If valine occupies a single series, the figures are at once inconsistent with regularity; but if, as they suggest, valine is present in both d- and L-forms and occupies two different series, then two distributions are possible (Table III).

If, therefore, the ratio of d- to L-valine should prove to be 1 : 4 or 4 : 1 the structure cannot be periodically regular; if 2 : 3 or 3 : 2 then regularity is possible.

In the latter case, the number of arrangements possible for an open chain is $4! \times 2! \times 3!$, and any of these is easily written down from the tree-diagram.

Conclusions.

This investigation shows the numerical conditions which must be fulfilled by a regular periodic structure, and leads to a simple diagrammatic method of testing which may be applied even to complex structures, provided that complete analytical data are available. Fulfilment of the conditions shows only that the data are consistent with regularity, which further evidence is needed to prove.

There emerges no suggestion that 2 and 3 hold any unique position as prime factors in the structure of a regular array of the type considered; if the hypotheses of Bergmann and Niemann should be proved to be correct, whether for proteins or for their sub-units, deeper insight into the structure and mode of formation of proteins will be needed to explain them.

I am grateful to Mr. Ivor Robinson for encouragement, and to Mr. C. H. Longuet-Higgins for bringing to my notice the question of series which have not a factor in common with all the rest.

¹⁰ Gordon, Martin and Syngle, *Bichem. J. (Proc. Biomed. Soc.)*, 1942, 36, xxi.

THE SOFTENING OF THERMOPLASTIC POLYMERS.

PART I.—THEORETICAL.

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One of the most important physical properties of thermoplastic polymers is their ability to flow readily at elevated temperatures under the application of a stress, and in point of fact this forms the basis of the plastics moulding industry. Hence, in order to obtain the correct moulding conditions for a given material, it becomes necessary to know something about its flow properties and more especially their variation with temperature. This is not only important for producing mouldings, but also for assessing their behaviour under stress at elevated temperatures

such as often occur under working conditions. To evaluate these properties, various empirical tests were devised and are now in use as routine control checks in the plastics industry; most of these aim at assessing the temperature at which some property of the raw material reaches an arbitrary value. This is known as the softening point, and has been used rather haphazardly to estimate both moulding conditions and heat distortion properties.

A discussion of some of these tests has been given by Couzens and Wearmouth.¹ With standardisation of testing procedure, the accumulation of precise data under known conditions has taken place, and hence it becomes possible to analyse the tests themselves more fully in the light of modern theoretical ideas on the mechanical properties of high polymers. An analysis on these lines is very necessary, as erroneous conclusions have sometimes been drawn from the results of some of these tests; this point has recently been emphasised by Gurevich and Kobeko,² who have reviewed the Martens heat test and Charpy impact test in terms of the theoretical work of Alexandrov and Lazurkin.³ In the following paragraphs the various softening point and flow-time tests are assessed in terms of modern theories, and some recent work on the flow properties of thermoplastics is discussed. Arising out of this, a general softening theory is developed; some experimental verification of it will be given in a subsequent communication.

Within the past decade, a number of softening-point tests have become standardised in various parts of the world. For illustrative purposes, two of these are described more fully here. In the modified Kraemer-Sarnow test,⁴ as used for characterising polyvinyl acetates and acetals, 10 g. of mercury are placed over a $\frac{1}{4}$ in. plug of the resin at the lower end of a 7 mm. tube. The temperature is raised at the rate of 4°C./min. , the softening point being defined as that temperature at which the mercury runs out. In the Martens test,⁵ a standard bar of material is deformed by a fixed cantilever load, the temperature being raised at a standard rate. The Martens degree of hardness is the temperature at which the deformation reaches a standard value—the A.S.T.M. heat distortion test⁶ has a similar basis.

It will be seen that both these and many other related tests all measure essentially the temperature at which a given deformation, simple or complex, is produced by a fixed stress. (The Rossi-Peakes test⁷ for injection and extrusion mouldings is based on a similar idea, but in this case a rate of deformation rather than a fixed value is specified.) Now, one point worth making at once is that, owing to the poor thermal conductivity (K) of thermoplastics, the temperature (T_s) may not be the actual specimen temperature; hence, not only will T_s for a given substance be dependent on the rate of rise of temperature (dT/dt) but comparative values of T_s for different substances at equal values of dT/dt might be misleading owing to different values of K .

The Complete Expression for D .

The generalised deformation (strain) produced in a specimen by a given stress will now be considered more fully. It can be analysed into three components which, in this simple treatment, will be treated as independent scalar quantities. These are:—

1. Viscous flow caused by the polymer chains sliding irreversibly over each other. If the polymer can be treated as a Newtonian liquid, we

¹ Couzens and Wearmouth, *J.S.C.I. (Trans.)*, 1942, 61, 69.

² Gurevich and Kobeko, *J. Tech. Physics, U.R.S.S.*, 1940, 9, 1267.

³ Alexandrov and Lazurkin, *Acta Physicochimica, U.R.S.S.*, 1940, 12, 647.

⁴ See, e.g., B.P. 436,072.

⁵ Wood, *I.P.I. Trans.*, 1937, 6, No. 12.

⁶ Am. Soc. for Testing Materials, Method D 48-39.

⁷ Peakes, *British Plastics*, 1934, 6, 421, 475, 516.

can express the viscous component (D_{visc}) in the form $A t e^{-\frac{E_{visc}}{RT}}$, A being proportional to the stress; the requisite values for A and E_{visc} are discussed later. If the polymer has a so-called "yield value," a more complex expression on the lines suggested by de Bruyne⁸ will be necessary.

2. Ordinary elastic deformation (D_{el}) due to a change in the equilibrium distance between chains and atoms. This has been discussed elsewhere.⁹ This has a Young's modulus which we denote by G_{el} .

3. Highly elastic deformation (D_{HE}) due to chain reorientation in the direction of applied stress. (For a discussion of this, see Mark.¹⁰) This has a low Young's modulus (G_{HE}) and a definite temperature dependence in contrast to G_{el} . We can write D_{HE} as a function of t in the usual form:^{10, 11}

$$D_{HE}(t) = D_{HE}(\infty) \left(1 - \exp \left(-\frac{t}{\tau} \right) \right)$$

where $D_{HE}(\infty)$ is the full highly elastic deformation for a given stress and τ is an orientation time, characteristic of the polymer.¹²

D_{el} is usually very much smaller than either D_{visc} or D_{visc} , and so is neglected; in the following paragraphs, the relative magnitudes of D_{visc} and D_{HE} are considered in terms of other variables, *viz.* time of loading, temperature, stress, total deformation (D), molecular size and structure. At constant stress, then, we put

$$D = D_{visc} + D_{HE}(t) \\ = A t e^{-\frac{E_{visc}}{RT}} + D_{HE}(\infty) \left(1 - e^{-\frac{t}{\tau}} \right) \quad (2)$$

$$= A t e^{-\frac{E_{visc}}{RT}} + D_{HE}(\infty) \frac{t}{\tau} \text{ for } \frac{t}{\tau} < 10^{-1}. \quad (3)$$

Thus, it is possible for the reversible highly elastic deformation to have the same dependence on time as the irreversible viscous component and hence to be confused with it. (In rubber, τ is very small at room temperature, $D_{HE}(\infty)$ being reached almost at once—thus, it is unnecessary to consider the time dependence of D_{HE} in the ordinary kinetic theory of rubber.) The composite character of the observed time-dependent deformation has led to much confusion in the past and to the introduction of the phrase "elastic after-effect" to explain any subsequent non-instantaneous decrease in deformation observed when the stress is removed. It follows from this that, in any static loading experiment, the slope of the linear portion of the $D - t$ curve is not necessarily a measure of the polymer viscosity and this assumption, as will be shown later, has led to erroneous estimates of this quantity.

In order to complete the preliminary development, it is necessary to analyse τ a little further. This quantity may be written in the form¹³

$\tau = U c^{\frac{1}{2}} \frac{R T}{U}$ where U is fairly large (50-100 k.cal.). A preliminary analysis of τ in terms of molecular structure, size and environment has been given elsewhere.¹¹ For unit stress, $D_{HE}(\infty) = \frac{1}{G_{HE}(\infty)}$, and both the Mark-

⁸ de Bruyne, *Proc. Physic. Soc.*, 1941, 53, 251.

⁹ Kuhn, *Z. physik. Chem. B*, 1939, 42, 1.

¹⁰ Mark, *Physical Chemistry of High Polymers*, Interscience, New York, 1941, pp. 69 *et seq.*

¹¹ Tuckett, *Trans. Faraday Soc.*, 1942, 38, 310.

* It is assumed here, for the sake of simplicity, that the $D_{HE} - t$ relation can be expressed in terms of a single orientation time. The introduction of a distribution in times about a most probable value does not alter the main conclusions.

Kuhn¹⁰ and Bresler-Frenkel theories¹¹ give $D_{\text{IN}}(\infty) = M/8$ where M is the molecular weight.* The variation in $G_{\text{IN}}(\infty)$, with temperature being small compared with that in the exponential term in eqn. (2), we can write

$$D = At e^{-\frac{E_{\text{visc}}}{RT}} + \frac{M}{8} \left[1 - \exp \left(-\frac{t}{B} \exp - \frac{U}{RT} \right) \right]. \quad . \quad (4)$$

This expresses D as a function of two independent variables, t and T . If, in any specific softening test, the temperature is being raised at a fixed rate ($dT/dt = \phi$), we can put $T = T_0 + \phi t$ and express D in terms of a single variable t .

$$D(t) = \int_0^t A \exp \left(-\frac{E_{\text{visc}}}{R(T_0 + \phi t)} \right) dt + \frac{M}{8} \left[1 - \exp \left(-\frac{t}{B} \exp - \frac{U}{R(T_0 + \phi t)} \right) \right]. \quad (5)$$

The softening point measures the temperature at which D reaches an arbitrary value, though it can equally well be defined as a time whose value is a solution of equation (5). The fundamental problem to be solved is the relative proportions of D_{visc} and D_{IN} in the total deformation, and this is considered further in the next section.

Dependence of D on t and T at Constant Stress.

In the previous paragraph a complete expression for D was derived, but this by itself is in rather an unattractive form, owing to the presence of a large number of constants which can only be evaluated from a variety of other physical measurements. As a casual inspection of this expression does not throw much light on the shape of the $D-T$ curve, we consider the variation of the component parts of D with time and temperature, which will be assumed initially to be independent variables.

(a) At constant temperature, the expression in eqn. (4) reduces to a fairly simple form

$$\begin{aligned} D(t) &= D_{\text{visc}} + D_{\text{IN}}(t) \\ &= at + \frac{M}{8} \left(1 - e^{-\frac{t}{B}} \right) \quad . \quad . \quad . \quad . \quad . \quad (6) \end{aligned}$$

which for $t \gg r$ becomes $at + \frac{M}{8}$. $D-t$ curves of this type are frequently encountered in any study of the extension of a strip of plastic under a fixed load. The important point, however, is that the elastic component reaches a static value $M/8$, whereas the viscous one increases linearly with time.

(b) At constant loading time, the variation of D with temperature is given by equation (4). In Fig. 1, D_{visc} and D_{IN} are plotted against T for a fixed loading time, t . Here again D_{IN} reaches a limiting value, $M/8$ † (corresponding to $t \gg r$) while D_{visc} increases, this time exponentially with T . If T varies with time in a linear manner, the slope of the $D-T$ diagram will be as in equation (5); the general variation of the two components with T will be similar to Fig. 1, but the slopes will be more sharp—the variation of D_{visc} with T will be more than exponential and D_{IN} will reach its limiting value within a smaller temperature interval.

Now, in Fig. 1, D_{IN} is drawn from Alexandrov and Lazurkin's data for methyl methacrylate, while D_{visc} is computed for an E_{visc} value of

¹¹ Bresler and Frenkel, *Acta Physicochemica U.R.S.S.*, 1939, 11, 485.

* δ is a constant. On the Mark-Kuhn theory,¹⁰ it has the value $2RT_0$, a being the density. Wall derives $2RT_0$ (*J. Chem. Physics*, 1942, 10, 485), and Frenkel predicts a value proportional to T_0^2 .

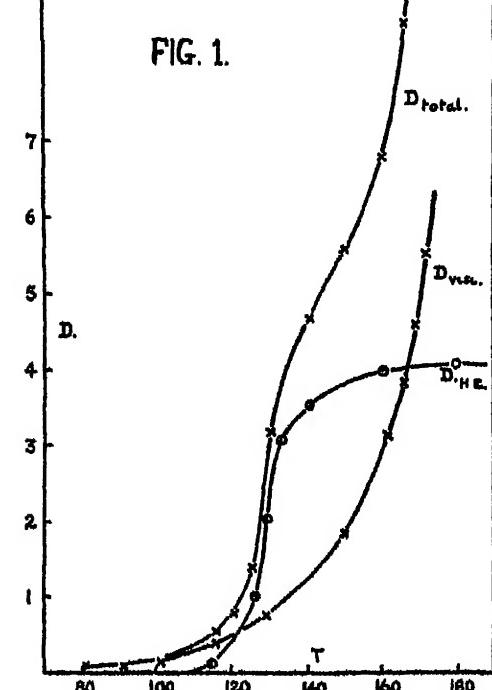
† δ does contain the temperature, but its dependency on T is slight in comparison with the exponential variation of D_{visc} .

20,000 cal., a fairly probable value. These have been superimposed on each other for the sake of clarity, but they might exist in quite different temperature regions, this circumstance depending on molecular structure and size. The correlation between structure and viscosity is still not clear, but an analysis of the effect of molecular weight on D_{visc} and D_m can be made. The viscosity of a polymer, as will be seen later, varies exponentially with the molecular weight so that an increase in average chain length will shift the D_{visc} - T curve towards higher temperatures while preserving its same general shape. The high elasticity temperature of a polymer, on the other hand, is determined by its orientation time, τ , which is chiefly a function of molecular structure.¹¹* Thus, the D_m - T curve will be in the same position though the limiting value of D_m , i.e.

$D_m(\infty)$, will increase with the degree of polymerisation.

Now, at the softening temperature, the total deformation reaches an arbitrary value, and it is obviously important whether this magnitude is greater or less than $D_m(\infty)$ for a given substance. Two cases will be considered.

(a) $D \sim D_m(\infty)$. It is clear that D might contain a considerable elastic component, and if the molecular size is such that when D_m starts developing $D_m \sim D_{visc}$, the total D will be almost entirely elastic, and hence any softening point determination of this type will be a measure of the elastic properties of a material rather than of its flow characteristics. Now this seems to be an important point to make, as the moulding temperature must be such that the deformation is almost



completely viscous, otherwise the final article on being removed from the cooled mould will be in a state of elastic strain. On heating, τ will decrease rapidly and the specimen will tend to return to its original shape; thus, a heat distortion test may give an anomalous result. This may lead to the rejection of a given polymer for a specific purpose, whereas it might have been quite satisfactory if made at a higher moulding temperature. Tests of the Martens type,¹ the A.S.T.M. heat distortion test^{*} and the Bureau

* Kirkwood and Fuoss (*J. Chem. Physics*, 1941, 9, 329; *J.A.C.S.*, 1941, 63, 2401), have recently predicted and found that the most probable electrical relaxation time in a polar polymer varies with the degree of polymerisation, but the temperature coefficient of the corresponding mechanical quantity is very high, and, in effect, the elastic temperature for a given polymer is little affected by molecular size. Kausmann has, however, queried the Kirkwood-Fuoss analysis (*Rev. Mod. Physics*, 1942, 14, 12).

of Standards softening point test, discussed by Wiley,¹³ all specify deformations of a loaded beam of material under conditions where D is probably largely elastic; hence the softening point and the so-called elastic transition temperature under these conditions are identical and not very dependent on molecular size. This has recently been demonstrated by Wiley¹³ for a number of substances. Tests of this type, then, cannot assess flow properties of the raw material for moulding purposes and their chief use is rather to specify the finished product.

(b) $D > D_{\text{in}}(\infty)$. A softening-point test which does not give misleading results for moulding purposes should give T as a function of D_{visc} rather than for D_{in} . This can be done by specifying a large deformation ($D \gg D_{\text{in}}(\infty)$) so that the elastic term is only a small part of the total deformation. This is done in the modified Kraemer-Sarnow and Rossi-Peakes tests, which, on the basis of the above reasoning, would give a more reliable estimate of flow properties for moulding purposes than the ones discussed in the previous paragraph; on these methods, softening points increase with molecular size, which is in accordance with our knowledge of flow processes in these systems.

Further Analysis of the Kraemer-Sarnow Data.

The next point is how to ascertain from softening point data as obtained by the Kraemer-Sarnow method whether elastic effects are present. To do this, the theory must be carried a little further; two cases are considered.

(a) D is almost wholly viscous: hence, attention must be focussed on the A and E_{visc} terms in D_{visc} , especially on their variation with molecular size. For a series of linear polyesters, Flory¹⁴ found the following empirical relationship between viscosity (η) and weight-average chain length (M_w).

$$\log \eta = \lambda + \mu(M_w)^k + \frac{E_{\text{visc}}}{RT} \quad \quad (7)$$

Flory's justification for using a weight-average molecular weight is not completely convincing, but the important point is that E_{visc} is independent of chain-length and only about 8 k.cal. in magnitude. A value of this order is found for rubber, and in general, E_{visc} for viscous flow in linear polymers without special bonds is believed to be $\sim 10-30$ k.cal. High values ($\sim 50-100$ k.cal.) are generally traceable to elastic effects as will be seen later.*

¹³ Wiley, *Ind. Eng. Chem.*, 1942, 34, 1052.

¹⁴ Flory, *J.A.C.S.*, 1940, 62, 1057.

* The restriction to linear polymers without special bonds (such as hydrogen ones) is necessary as many glasses and non-linear phenol-formaldehyde resins have high values (~ 100 k.cal.) for E_{visc} (e.g. Hartshorn, Megson and Rushton, *Proc. Physic. Soc.*, 1940, 52, 796; Taylor and Doran, *Glass Ind.*, 1939, 20, 173; 1941, 24, 103). For the moment, however, we assume that in linear polymers U is greater than, and different from, E_{visc} ; the direct experimental demonstration of this is not absolutely complete as E_{visc} is usually measured at a higher temperature than U and increases with decrease of temperature (e.g. Flory, ref. ¹⁴, Ferry and Parks, *Physics*, 1936, 6, 356). For rubber, however, the distinction seems fairly clear-cut as values at room temperatures have been compared (Eley, *Trans. Faraday Soc.*, 1942, 38, 303). Indirect evidence also comes from electrical measurements. It will be shown in a forthcoming paper that dielectric relaxation in polar polymers is intimately connected with highly elastic orientation and not with the macroscopic viscosity of the system; the latter, however, can be compared with the D.C. conductivity (Preston, *J. Appl. Physics*, 1942, 13, 625). Hence, it seems profitable to compare E -values for D.C. conductivity and dielectric relaxation in linear polar polymers. This has been done by Kauzmann (*Rev. Mod. Physics*, 1942, 14, 35, Table IV). The distinction between the two electrical processes is shown and thus indirectly that between the two mechanical ones also.

If viscosity can be treated as a rate-process,¹⁵ η for a simple liquid can be written in the form $\frac{Nh}{V} e^{-\frac{\lambda S}{R} + \frac{AH}{RT}}$. On this basis, Kauzmann and Eyring¹⁶ have considered the motion of long chain molecules in terms of the segmental theory of flow of these substances; an expression of the same form as the empirical one of Flory is obtained, the constants λ and μ being evaluated more explicitly. Now the Flory equation can be applied directly to softening point data, for if D is almost wholly viscous, softening points can be treated as roughly iso-viscous temperatures (T_s) at which η has a fixed value depending on the test conditions; its absolute value is immaterial, but probably in the region 10^6 - 10^7 poises for the conditions of the Kraemer-Sarnow test. Hence, for a series of polymers from the same monomer unit but of differing molecular size, we can put:

$$\mu \sqrt{M_w} + E/RT_s = \text{const.} \quad (8)$$

This can be regarded as an equation connecting two variables, softening point and molecular weight; hence, the plot of $1/T_s$ against $\sqrt{M_w}$ ($= \sqrt{v}$), the quantity measured by the Staudinger method, should be a straight line. This has been done in Fig. 2 for a number of commercial

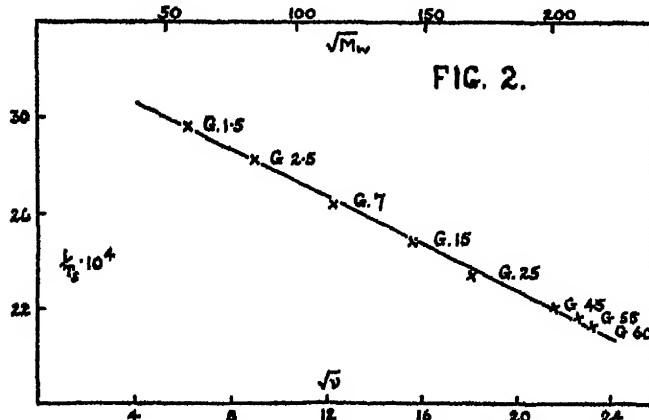


FIG. 2.

polyvinyl acetates, the T_s values being taken from Morrison's recent paper;¹⁷ † the range of molecular weight is from 3,400 to 46,000 and the points lie on a fairly good straight line, so that under these conditions the softening deformation is largely viscous. The slope of the line is also in rough agreement with theory, it being given by $E_{visc}/R\mu$; assuming $E_{visc} = 23.0$ k.cal.,¹⁸ this gives a μ value of 0.40. Flory finds $\mu \sim 0.17$ for his linear polyesters, while Kauzmann and Eyring predict 0.25.

(b) D is partly viscous and partly elastic. It is assumed that the measured T_s is much higher than that at which high elasticity develops, so we may write, as in eqn. (6), ignoring the variation in t :

$$D = D_{visc} + D_{el}(t) \\ = k \exp \left(-\mu \sqrt{M_w} - \frac{E_{visc}}{RT_s} \right) + \frac{M_w}{t} \quad (9)$$

¹⁵ *The Theory of Rate Processes*, Glasstone, Laidler and Eyring, McGraw Hill, New York, 1941, pp. 477 et seq.

¹⁶ Kauzmann and Eyring, *J.A.C.S.*, 1940, 62, 3113.

¹⁷ Morrison, *Chem. Ind.*, 1941, 60, 387.

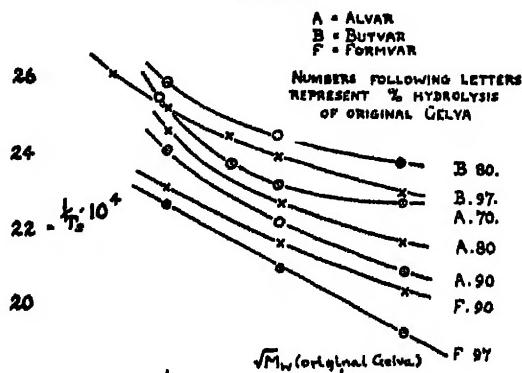
† The molecular weights used are not those of Morrison but more accurate ones from a private communication from Shawinigan Ltd.

¹⁸ Part II of this series. To be published later.

Hence, as molecular size increases the elastic component forms a larger portion of the total deformation, and this will have an increasingly depressant effect on T_g so that the $1/T_g - \sqrt{M_w}$ line will become curved upwards. This is seen in Fig. 3, where data¹⁹ for a number of polyvinyl formals, acetals and butyral all derived from polyvinyl acetates, but of various degrees of acetalation, are plotted.

The deviations are all in the right direction, and it is interesting to note that the curvature becomes less pronounced as the degree of replacement increases; this is best seen in the three Alvar series and in the Formvar 97 set, a return to a linear relationship is found. The reason for this can be understood roughly. It is experimentally observed that the replacement of acetate groups by acetal ones cuts down cold flow and hence decreases D_{visc} ; this acts in two ways. Primarily, T_g is raised, but also the $1/T_g - \sqrt{M_w}$ line becomes a curve for the reasons given above. This is most pronounced in the Alvar-70 series. Now, as replacement of acetate groups continues, D_{visc} is reduced still further, partly as a result of occasional cross-linking, and hence, to produce a given total deformation, the temperature needs to be raised. Now, as D_{visc} increases exponentially with T while $D_{m(\infty)}$, which is assumed roughly constant during acetalation, is little dependent on it (eqn. (4)), a rise in temperature increases the proportion of D_{visc} once more and straightens out the $1/T_g - \sqrt{M_w}$ curve as in the Formvar-97 series. If, then, mouldings are made on the basis of T_g values, the curvature of the $1/T_g - \sqrt{M_w}$ relationship will give indication of the relative degree of elastic strain in the finished product.

FIG. 3.



Dependency of D on Load.

So far the dependence of D on the stress has not been considered; this is obviously important as this latter factor is markedly affected not only by the load but equally by the dimensions of the specimen. If the test conditions are altered, T_g will only be the same if both D_{visc} and $D_{m(\infty)}$ have the same dependency on the applied stress. This may not always be so for two reasons:

1. A non-linear dependency between stress and elastic strain (D_{visc}), i.e. $G_{visc}(\infty)$ is a function of stress. Wall²⁰ has recently predicted such a relationship.

2. A non-linear relation between stress and D_{visc} , due either to non-Newtonian flow or to the existence of a so-called "yield-point."

For small deformations, (1) is probably not important, but (2) applies whatever the magnitude of D . The existence of a definite yield-value in amorphous plastics is still a debatable point though a critical creep

¹⁹ Shawinigan Ltd., Technical literature.

²⁰ Wall, *J. Chem. Physics*, 1942, 10, 132.

stress is often found; on the theoretical side, the considerations of Kauzmann and Eyring¹⁶ and de Bruyne⁸ have indicated possible mechanisms which are not necessarily mutually exclusive--from the experimental viewpoint, much of the data seems unreliable, though Couzens and Wearmouth¹ have recently given fair evidence for its existence in a polyvinyl chloride-acetate co-polymer.

Now, a yield value is usually associated with a breakdown or change of structure, as implied by Houwink,²¹ and it might be significant that in plastic materials where its existence is claimed, there is often some indication of the presence of crystalline regions, either as a consequence of the basic molecular structure or as a result of the method of preparing the specimen—for example, in sheet material, the chains are often preferentially orientated in one direction by the rolling process. In cellulose acetate and nitrate, both effects can contribute to produce crystalline regions and it is in these systems that yield-values are often found. In a truly amorphous polymer without special bonds, its existence seems more doubtful.

These considerations are obviously important in assessing the dependence of softening points on stress. If the latter is below F_0 , the yield-value of the material, D_{visc} , is zero and D is entirely elastic. Above F_0 , the proportion of D_{visc} increases steadily with F . It will be readily seen that effects such as these might lead to a fallacious assessment of flow properties, and this has recently been demonstrated by Couzens and Wearmouth¹ for three specimens of cellulose acetate using a modified Martens test.

The Experimental Determination of Flow Properties.

Under the conditions of a true softening-point test, it may be generally assumed that any highly elastic component is attained quickly at $T = T_g$, i.e., $\tau \ll 1$ sec. Many static loading experiments on the flow properties of thermoplastics are, however, often performed at temperatures where τ is greater than the loading time, the total deformation or its rate being measured. Under these conditions, we have by an extension of eqn. (3):

$$D = D_{visc} + D_{im}(t) \\ = At \cdot e^{-\frac{E_{visc}}{RT}} + D_{im}(\infty)B^{-1}t \cdot e^{-\frac{U}{RT}} \quad . \quad . \quad . \quad (10)$$

Hence dD/dt is of the form $k_1 \cdot e^{-\frac{E_{visc}}{RT}} + k_2 \cdot e^{-\frac{U}{RT}}$, where in general E_{visc} and U have very different values ($U > E_{visc}$). Now, if D_{im} starts developing before D_{visc} (see Fig. 1) the measured energy of activation, obtained from $d \ln D/d(t/T)$, will be U as the deformation is largely elastic. At higher temperatures, however, equation (10) does not apply as $t \gg \tau$ and the variation in D is almost wholly due to the change in D_{visc} . In this region, then, the energy of activation will correspond to E_{visc} and have a much smaller value. This is seen best in Wiley's results;²² on so-called viscous flow in some thermoplastics. From his experimental set-up, it is clear that viscous and elastic effects have not been separated. His results enable log "viscosity" $-1/T$ plots to be made. These are pronounced curves over a relatively small temperature range, indicating at once that a composite process may be involved. For a given cellulose acetate, the slopes of these curves at high temperatures are ~ 20 k.cal. and ~ 70 k.cal. at temperatures $\sim 40^\circ$ lower; this is exactly what might be expected on the basis of the theory outlined above. It might, of course, be argued that this change is due to an alteration in E_{visc} with temperature, but,

²¹ *Elasticity, Plasticity and Structure of Matter*, Houwink, Cambridge, 1937.
²² Wiley, *Ind. Eng. Chem.*, 1941, 33, 1377.

from the limited data available on other systems, this effect by itself does not seem large enough to explain the variation experimentally observed. The high temperature value of ~ 20 k.cal. is probably a true one for E_{visc} as it is similar to that for unplasticised polyvinyl acetate.¹³ The same author¹³ has recently also made the suggestion that softening points represent *iso-viscous* states but also identifies them with elastic transition temperatures. The analysis of the previous sections has shown that both these cannot be true simultaneously for a specific test and an examination of the test methods which he considers (the A.S.T.M. heat distortion and the Bureau of Standards softening point test) show that, as small deformations are specified, elastic properties only are probably being computed—hence, his estimate of 10^{11} - 10^{12} poises for the softening viscosity may be quite erroneous.

Viscosity estimates for various thermoplastics have also been made by Kistler.¹³ Here again viscous and elastic components are not completely distinguished though their existence is indicated. For polyvinyl acetates at $40^\circ C.$, E_{visc} values of 60-80 k.cal. are obtained from the increase in length of strips at constant stress over a small temperature range. This might be expected, as in this range this polymer is just developing its elastic properties. At corresponding elastic temperatures cellulose acetate, methyl methacrylate and polyvinyl formal give E values of 100-170 k.cal. For natural and synthetic rubbers, much lower E values are found (~ 30 k.cal.), and these may be nearer the true values as these experiments are done at $25-30^\circ C.$ which is well above the elastic transition temperature for these substances. The experiments of Ueberreiter¹⁴ suffer from similar interpretational defects.

Recently, the parallel plate plastometer has been used to get some idea of the softening range of thermoplastics. For a given load, Wearmouth and Small¹⁵ have calculated a "yield-value" from the limiting thickness of a specimen compressed between the plates of such an instrument. For a number of synthetic substances this quantity has been plotted against temperatures and shows a sharp decrease in value over a small range. In view of the ideas developed in this paper, it seems that an

alternative interpretation of these results can be proposed. The limiting thickness taken up by the specimen roughly represents the equilibrium deformation produced by a given load; this varies roughly with the overall Young's modulus (G) at the particular temperature. Hence, in reality, the curves show a sharp drop in G over a small temperature range. In Table I are set out these transition temperatures (T_s) for the materials studied by Wearmouth and Small. This sudden fall in G is typical of the change that occurs over a small temperature range from a small ordinary elastic deformation to a large highly elastic one; it does not necessarily have any direct connection with the true *iso-viscous* softening temperature discussed in the previous section; it is, however, the same as the softening point as measured by any "small deformation" method, in which case it is a measure of the elastic, rather than the flow properties of a material. The fact that Wearmouth and Small's T_s values are in rough agreement with their elastic transition temperatures, so far as they are known at the present, makes this explanation fairly likely.

TABLE I

Substance.	T_s °C.
Polyvinyl acetal . .	50
" formal . .	115
" chloride . .	118
Polystyrene . .	85

¹³ Kistler, *J. Appl. Physics*, 1940, 11, 769.

¹⁴ Jenckel and Ueberreiter, *Z. physik. Chem. A*, 1939, 182, 361.

¹⁵ Wearmouth and Small, *Brit. Plastics*, 1941, 12, 377.

Summary.

The general deformation produced in an amorphous high polymeric material by a given stress is analysed into its three components which are termed ordinary elastic, highly elastic and viscous. These all have different dependencies on molecular size, structure, temperature and duration of stress—the effect of these variables is worked out and the information obtained is used to analyse the various empirical softening point tests which are in current use to characterise plastics. It is shown that such tests fall into two main groups: (1) Those which measure the slow properties of materials and, as such, are of use in evaluating correct moulding conditions. (2) The second class essentially measures the temperature at which high elasticity develops—this is important in assessing heat distortion properties of the material under working conditions. A typical flow-property test, the modified Kraemer-Sarnow, has been analysed further and, on the assumption that softening points of this type are essentially iso-viscous states, a relation between molecular size and softening temperature, based on Flory's relationship, has been predicted and shown to hold experimentally in the case of the polyvinyl acetates. Deviations that occur with other materials are explained qualitatively. Finally, a critical survey of several recent estimates of polymer viscosities has been given, it being shown that the viscous properties of such systems have often been confused with highly elastic ones.

This work has been carried out in the Department of Colloid Science, Cambridge, and I should like to record here my best thanks to Professor E. K. Rideal for many stimulating discussions during the period in which the ideas expressed above have been developed. I am also grateful to members of other laboratories for helping me to clarify this manuscript prior to publication.

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A NOTE ON UNIMOLECULAR REACTIONS.

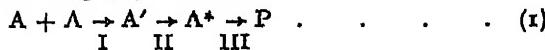
By D. D. ELLY.

Received 16th March, 1943.

The purpose of this note is to discuss briefly certain aspects of the modern theory of unimolecular reactions, which become increasingly important as the theory is extended to include within its scope such processes as viscous flow, elastic and dielectric relaxation in condensed systems. I am concerned mainly with examining the application of the "square-term" and "transition-state" formulae to rapid reactions. While these formulae are well-known and widely used, I do not know of any detailed discussion of their respective ranges of application, although the theoretical basis for such a discussion has already been provided in the papers by Eyring, and Evans and Polanyi.

Consider a unimolecular reaction, $A \rightarrow P$, which we take to include any process involving the passage of the system A over an energy barrier

(e.g. as in Eyring's theory of liquid viscosity¹). The process may then be divided into a number of steps, symbolised as



Step I.—This concerns the collisional activation of A; by means of collisions the molecule A gains the necessary critical energy for reaction (Lindemann theory). We are particularly concerned in this note with condensed systems, where all the neighbouring molecules may be concerned in the collisional activation. For such systems we may reasonably assume step I to be the fastest process of the three, and we shall not discuss it any further (nor the reverse process of de-activation).

Step II.—Here the molecule A', which contains the excess energy E (activation energy) spread over s "square terms" ($s/2$ vibrational degrees of freedom) after a certain interval of time becomes "reactive." That is, the energy E comes into the bond or bonds that are to be activated, and the system reaches the top of the potential barrier, where it may be designated the activated complex A^* .²

Step III.—The activated complex passes over the barrier (i.e. decomposes, or otherwise reacts).

There are two cases, then, of prime interest in condensed systems. In the first case step II is rate-determining, and in the second step III. It is important to realise exactly what formulae apply to each step, and their limitations.

Step II. is Rate-Determining.—The rate of step II is then best evaluated by solving the equations deduced by Tolman³ for the case of a uni-molecular gas reaction at high pressure (i.e. where collisional activation, step I, is faster than the rate of reaction, which is the case of interest to us). This equation is

$$k = \frac{\sum k_i p_i e^{-\epsilon_i/kT}}{\sum p_i e^{-\epsilon_i/kT}} \quad \quad (2)$$

Here each molecule with energy ϵ_i , statistical weight p_i , is regarded as possessing a specific rate constant k_i . The suffix "j" refers to activated molecules, "i" to all molecules. The observed first order constant k is thus obtained by averaging the molecular rate k_i by the usual method of statistical mechanics.

This equation appears to have been solved in two approximations.

First approximation (Hinshelwood, Fowler and Rideal⁴),

$$\begin{aligned} k_i &= 0 \quad \text{when } \epsilon_i < \epsilon \\ k_i &\rightarrow \lambda \quad \text{when } \epsilon_i > \epsilon. \end{aligned}$$

$$\text{Then } k = \lambda \left[\frac{1}{(s/2 - 1)}! \left(\frac{\epsilon}{kT} \right)^{s/2 - 1} \right] e^{-\epsilon/kT} \quad \quad (3)$$

It is important to realise, as Fowler and Guggenheim have pointed out, that this much-used formula is valid only for $\epsilon \gg s/2 kT$ when s is the number of square terms.

Second approximation (Rice and Ramsperger, Kassel⁴).

Here the transformation probability of a molecule k_i is considered to increase with the excess of energy that the molecule possesses over the

¹ Glasstone, Laidler and Eyring, *The Theory of Rate Processes*, McGraw-Hill, 1941.

² Tolman, *Statistical Mechanics*, p. 259, Chemical Catalogue Co., 1927.

³ See Guggenheim and Fowler, *Statistical Thermodynamics*, p. 522, Cambridge, 1939.

⁴ See Kassel, *Kinetics of Homogeneous Gas Reactions*, p. 93, Chemical Catalogue Co., 1932.

minimum activation energy ϵ_m . For reaction there must be at least m quanta ($\epsilon_m = m\hbar\nu$) in the one degree of freedom that is to react. Then if the total number of quanta spread over all degrees of freedom of the molecule is j , then the probability of m in the particular degree of freedom, i.e. k_j , increases with ($j - m$). This leads then to the simple equation

$$k = A e^{-m\hbar\nu/kT} \quad \quad (4)$$

where A has the dimensions of a frequency, like λ in equation (3).

It is difficult at the present time to assess the respective merits of the formulae (3) and (4) as applied to gaseous reactions, since so many of these during recent years have been shown to be complicated by chain reactions.⁵ The theory of the second approximation is considered by Kassel to give a better account of the way k falls off with pressure decrease, in certain instances. Hinshelwood,⁶ on the other hand, considers the first approximation to describe the experimental results within our present knowledge. There is, however, one point that seems to be missed. A , in equation (4), and λ in equation (3), both describe the probability with which energy spread over the whole molecule will concentrate in the bond that must be activated to form the activated complex A^* . This probability has been calculated, first by Polanyi and Wigner,⁷ and more recently by Slater,⁸ and comes out to be of the order of an atomic vibration frequency, 10^{12} sec.⁻¹. The formula (4), $k = A e^{-E/RT}$, is conventionally used to describe unimolecular reactions (condensed phase, or high-pressure gas reactions), and the first authors showed that in the large majority of cases experimentally $A \sim 10^{12}$ sec.⁻¹ in agreement with their theory. If, however, equation (3) be applied to the experimental data, using s obtained from the point at which k starts to fall off with pressure decrease, λ comes out to be $10^6 - 10^8$ sec.⁻¹, which is not in such good agreement with theory as the previous case.⁹ However, it is not legitimate to make any conclusion in favour of equation (4) on these grounds, since it is likely that in many of the experiments reviewed step III and not step II is rate-determining, and in this case this theory is not to be regarded as applicable.

In the following discussion we shall consider equation (3), since this has found a widespread application in the literature of "fast" reactions in solution, i.e. reactions with $A > 10^{12}$ sec.⁻¹. In describing such reactions it has become a frequent practice to take λ as about 10^{-12} sec.⁻¹ and to adjust s to give the right value of A in the empirical equation $Ae^{-E/RT}$.

Step III is Rate-Determining.—The equations for this case, probably the most usual, have been developed through the activated complex theory of Eyring, and Evans and Polanyi.¹ In this case the activated complex A^* may be considered to be in equilibrium with the initial reactant molecule A , and to react with a frequency kT/h sec.⁻¹. Briefly if K^* be a special form of equilibrium constant relating to the activated complex A^* and the reactant A , then in the simplest instance

$$k = \frac{kT}{h} \cdot K^* \quad$$

or in the convenient thermodynamic notation

$$k = \frac{kT}{h} e^{\frac{4S^*}{R}} e^{-\frac{4H^*}{RT}} \quad \quad (5)$$

⁵ Discussion in *J. Chem. Physics*, 1939, 7, 749.

⁶ Hinshelwood, *The Kinetics of Chemical Changes*, Oxford, 1940, p. 79.

⁷ Polanyi and Wigner, *Z. physikal. Chemie*, A, 1928, 139, 439.

⁸ Slater, *Proc. Camb. Phil. Soc.*, 1939, 35, 56.

At normal temperatures $\frac{kT}{\hbar} \sim 10^{12}$ sec.⁻¹, and if $\Delta S^* > 0$ we may again have fast reactions, i.e. those where $A > 10^{12}$ sec.⁻¹.

It is important to realise that formula (5) applies to the case where A and A^* are in equilibrium, i.e. where steps I and II are much faster than III. It therefore considers k to be a function of a ratio probability of $A^*/\text{probability of } A$, as expressed either through K^* or ΔS^* . On the other hand, in formula (3) the probability of the activated state is ignored. Here one is concerned only with the probability of the preactivated state A' , multiplied by a λ which is to be calculated from mechanics (or more strictly quantum mechanics) and not statistical mechanics. If step II is rate-determining and formula (3) holds, then the equipartition of energy is not to be regarded as holding in A^* , and accordingly the statistical-mechanical probability of A^* does not enter into our equations, but only that of A' . If step III is rate-determining, then we may regard the equipartition law to hold for all bonds in A^* except that which is actually broken, and K^* and ΔS^* are calculated in this theory using the ordinary partition functions.

Experimental Criterion.—It is the purpose of this paper to note a possible experimental criterion between the two cases, formulated in equation (3) and (5) respectively. We shall discuss this with particular regard to the case of "fast" reactions. It resides in a measurement of $\frac{\partial E_{\exp}}{\partial T}$ where E_{\exp} is the Arrhenius energy of activation

$$E_{\exp} = RT^* \frac{\partial \ln k}{\partial T}.$$

Equation (3) is well known to give $E_{\exp} = Ns - N(s/2 - 1)kT$

and $\frac{\partial E_{\exp}}{\partial T} = -N(s/2 - 1)k = -(s/2 - 1)R,$

i.e. it is always negative, and the faster the reaction (i.e. the larger A , therefore the larger s), the larger will be $-\frac{\partial E_{\exp}}{\partial T}$.

Equation (5), on the other hand, gives

$$\begin{aligned} E_{\exp} &= RT + \Delta H^* - p\Delta V^* \\ &= RT + \Delta E^* \end{aligned}$$

(ΔV^* = volume change of activation, ΔE^* = corresponding change of internal energy)

whence $\frac{\partial E_{\exp}}{\partial T} = R + \left(\frac{\partial \Delta E^*}{\partial T}\right)_V = R + \Delta C_V^*.$

Now ΔS^* is connected with ΔC_V^* (the heat capacity of activation) by the conventional equation

$$\Delta S^* = \int_0^T \Delta C_V^* d \ln T.$$

So, since high A factors mean positive values of ΔS^* these must be associated with positive values of $\partial E_{\exp}/\partial T$.

Physically the reason for this difference in behaviour resides in the considerations mentioned above: formula (5) takes into account the probability of the activated state and therefore the heat capacity of its bonds, whereas formula (3) does not do so.

An Erroneous Application of the "Square-Term" Formulation.—Equations (3) and (5) have both been used by the protagonists of the respective theories to analyse the same body of data, and it is not my purpose at the present time to attempt to decide in any case which is the most

suitable. As pointed out above, this is perhaps best done through a measurement of $\frac{dE_{\text{exp}}}{dT}$ (usually not easy to carry out, unfortunately). However, there is one way in which equation (3) is manipulated which seems

definitely erroneous. If the function $\left(\frac{E}{RT}\right)^{\frac{s}{2}-1} \left(\frac{1}{s/2-1}\right)$ for any arbitrary E/RT be plotted against s a maximum value may be obtained. This is a matter of some interest for the rate properties of polymers, such as viscous flow, since it appears to provide a theoretical basis for the empirical theory of "Segment-flow," suggested by Eyring.¹ However, as Fowler and Guggenheim² point out, the equation (3) is valid only for $E/RT \gg (s/2 - 1)$, and the maxima occur just in this region (*i.e.* at values of $s/2$ given by $E/RT = s/2 - 1$). Accordingly, we must regard all considerations of viscous flow in polymers, or the chemical stability of chain molecules, based upon such a treatment of equation (3), as invalid.

Summary.

The applicability of well-known formulae to the case of unimolecular reactions is critically discussed. In the interesting case of fast reactions, *i.e.* where $A > 10^{15} \text{ sec.}^{-1}$ in $k = Ae^{-E/RT}$, and experimental criterion is given to decide whether or not the fluctuation of energy inside the large molecule is the rate-determining step. If it is, $\frac{dE_{\text{exp}}}{dT}$ should be negative, while if it is not, $\frac{dE_{\text{exp}}}{dT}$ should be positive, and the transition state theory applicable.

An erroneous application of the "square-term" formula is pointed out.

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THE KINETICS OF HAEMOGLOBIN REACTIONS.

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During recent years several authors have discussed the kinetics of enzyme reactions. Moelwyn-Hughes^{1, 2} was concerned with the application of the collision theory of chemical reaction, and later developed chain mechanisms to explain cases where the rate was faster than this theory would predict. Stearn³ made use of transition-state theory, using the concept of "outcrop of activation" to explain rapid reactions. All work in this field, however, suffers through a lack of precise knowledge concerning the concentration or activity of enzymes. Because of this lack of knowledge the following study of haemoglobin was undertaken. Haldane⁴ has pointed out the analogy between the reaction of haemoglobin with oxygen or CO, and the reaction of an enzyme with a substrate. Haemoglobin is, in fact, a close chemical relation of many enzymes, *e.g.* peroxidase, catalase and cytochrome oxidase. The concentration of haemoglobin may be defined and measured with a clarity not possible in most enzyme systems, and there exists for it a wide range of rate and equilibrium data, the result of the accurate experimental work of Hartridge and Roughton.

¹ Moelwyn-Hughes, *Ergeb. Enzymforschung*, 1933, 2, 1.

² Moelwyn-Hughes, *ibid.*, 1937, 6, 23.

³ Stearn, *ibid.*, 1938, 7, 1.

⁴ Haldane, *Enzymes*, Longmans, 1930.

The object of this paper, then, is to re-examine the rate-measurements of Hartridge and Roughton, with particular reference to the constants of the corresponding equilibria. Such a treatment is conveniently formulated in terms of the transition-state theory of reaction-rates, firstly because this theory emphasises the connection between rates and equilibria, and secondly because it allows a ready consideration of the many complicating factors that may attend the reactions of large protein molecules in solution. We shall discuss only certain outstanding features of these reactions, which are of general interest. It will be seen that there are many points of detail which require to be cleared up by further experimental work.

Kinetic Equations and Data.

The conventional expressions are used for the specific rate constant, k .

$$k = A c \cdot e^{-E/RT} = \kappa \frac{kT}{h} e^{\frac{\Delta S^*}{R}} e^{-\frac{\Delta H^*}{RT}}$$

The first equation is the empirical equation, where A is the so-called "temperature-independent" factor, and E the activation energy, calculated in the usual way as $RT^2 \partial \ln k / \partial T$. The second equation is a transition-state theory formulation,^{5, 6} where ΔS^* and ΔH^* are the entropy change and heat content change respectively, on forming the activated complex from the reactants, all species being in their standard states. The standard state used throughout this work is a concentration of one mole per litre. The factor κ , the transmission coefficient, is assumed to be unity in accordance with the usual practice (this will be commented upon later in the paper). Values of E and ΔH^* are expressed in cal. per mole, and of ΔS^* in cal. per degree per mole (shortened to E.U., entropy units).

Reaction rates are classified as normal, or otherwise, according to the value of A . For reactions in solution it may be shown that $E = \Delta H^* + RT$

and therefore $A = e^{-kT} e^{\frac{\Delta S^*}{R}}$ (p. 199¹⁰). A normal unimolecular reaction

may then be conveniently defined as one for which $\Delta S^* = 0$, giving $A = 1.7 \times 10^{11}$ sec.⁻¹ at 293° K. (a value close to that most frequently found experimentally, cf. Polanyi and Wigner⁷). For a bimolecular reaction, the normal reaction is defined as one for which $A = Z$, the collision number as calculated by kinetic theory.⁸ If the rate constants are given in litre mole⁻¹ sec.⁻¹, the corresponding value of Z is 10^{11} , and therefore the normal bimolecular reaction has $\Delta S^* = -5.7$ E.U.

Reactions for which the experimentally determined values of ΔS^* are greater than the above are described as "rapid reactions," and where ΔS^* assumes large negative values, as slow reactions. For slow bimolecular reactions the steric factor $P(A = PZ)$ may be used. In Table I we summarise the kinetic data of Hartridge and Roughton in terms of ΔS^* . Hb symbolises haemoglobin, HbO₂ oxyhaemoglobin, etc., the molecular weight being taken as 16,700, the Fe-equivalent, for the purposes of kinetic calculations. The molecule of haemoglobin has, in fact, a M.W. of 68,000, and contains 4 atoms of Fe. In a part of the discussion we shall wish to take this specifically into account, when we shall symbolise haemoglobin as Hb₄.

⁵ Evans and Polanyi, *Trans. Faraday Soc.*, 1935, 31, 875; 1937, 33, 448.

⁶ (a) Eyring and Wynne-Jones, *J. Chem. Physics*, 1935, 3, 493; and other papers by Eyring, cf. ref. 6(b). (b) Glasstone, Laddler and Eyring, *The Theory of Rate Processes*, McGraw Hill, 1941.

⁷ Polanyi and Wigner, *Z. physikal. Chemie*, 1928, 139, 439.

⁸ Hinshelwood, *The Kinetics of Chemical Change*, Oxford, 1940.

TABLE I.*

Reaction.	Type.	ΔH^*	ΔS^*	pH effect	Ref.
1a. $HbO_2 \rightarrow Hb + O_2(aq)$.	Unimol.	25,000	30	At 5.6	9
		22,400	24	At 9.0	9
1b $Hb + O_2(aq) \rightarrow HbO_2$.	Bimol	0	30	None	10
2a. $HbCO \rightarrow Hb + CO(aq)$.	Unimol.	22,400	11	V. small	11
2b. $Hb + CO(aq) \rightarrow HbCO$	Bimol	0,100	2	V. small	12
3. $CO(aq) + HbO_2 \rightarrow HbCO + O_2(aq)$	Bimol	16,000	14	—	13

* The ΔS^* and ΔH^* refer to gases in their standard state of 1 mole per litre in solution in water.

Discussion of Reaction Rate Data.

A few explanatory comments on Table I are necessary. The dissociation of HbO_2 has a rate independent of pH in alkaline solutions up to pH 8, when it increases 7-fold over the range pH 8 to pH 6, at which pH again there are indications of a constant rate independent of pH being reached. Hartridge and Roughton⁹ attribute the slower rate at pH 9.0 ($\Delta H^* = 22,400$, $\Delta S^* = 24$) to the ionised form of oxyhaemoglobin, i.e. oxyhaemoglobin that has dissociated one hydrogen ion per hem (the so-called oxy-labile acid group, or haem-linked acid group). The higher rate at pH 5.6 is attributed to the unionised oxyhaemoglobin, and their value for the acid dissociation constant of 2×10^{-7} derived from the pH-reaction rate curve is in good agreement with more recent values from other sources.¹⁴ We note that the higher rate (at pH 5.6) has the higher activation energy, the effect, so far as can be seen, being outside the experimental error. The higher rate in this solution is due to the higher value of the entropy of activation ΔS^* .

The importance of ΔS^* for the *dissociation reactions* appears in other ways besides that just mentioned. It is clear that the characteristic rapidity of the HbO_2 dissociation is due to the high ΔS^* value, rather than a low value of activation energy or ΔH^* . Comparing this dissociation with that of $HbCO$, which is 10^4 times slower, we see the two reactions have the same ΔH^* value. The decreased rate in the latter case is due to the smaller ΔS^* value, which is therefore responsible for the increased stability of $HbCO$ over HbO_2 . It is possible that a similar explanation holds for the poisoning action of CO on myoglobin, cytochrome oxidase, etc. To decide whether this is so will require accurate measurements of the temperature coefficients of the rates of these systems not easy to carry out in practice.

Very large ΔS^* values have already been reported for protein reactions such as denaturation, and enzyme-inactivation^{8, 15} (~ 100 E.U.). The rates concerned, however, were dependent on a high power of the pH, and it has been pointed out,¹⁶ that if allowance be made for the acid ionisation of the protein, then the ΔS^* values reach the normal small value. The

⁸ Hartridge and Roughton, *Proc. Roy. Soc. A*, 1923, 104, 395.

¹⁰ Hartridge and Roughton, *ibid.*, 1925, 107, 654.

¹¹ Roughton, *Proc. Roy. Soc. B*, 1934, 115, 473.

¹² Roughton, *ibid.*, p. 470.

¹³ Hartridge and Roughton, *ibid.*, 1923, 94, 336. See also Roughton, ref. 12,

P. 451.

¹⁴ Coryell and Pauling, *J. Biol. Chem.*, 1940, 132, 760.

¹⁵ Stearn and Eyring, *J. Chem. Physics*, 1937, 5, 113.

¹⁶ La Mer, quotes Steinhardt, *Trans. Faraday Soc.*, 1938, 34, 71.

data of Table I, including that for the dissociation of oxyhaemoglobin, are independent of p_{H} and therefore require no such correction. (For HbO_2 the effect of p_{H} has already been considered, the two ΔS^* values referring to the unionised species ($\Delta S^* = 36$) and the ionised species ($\Delta S^* = 24$)).

Exactly the reverse conclusion holds for the *association* reactions. The high rates here observed are due to low values of the activation energy, ΔH^* , rather than to high values of ΔS^* . The $\text{Hb} + \text{O}_2$ reaction has, in fact, a large negative ΔS^* value. Conventionally, it might be argued that this small steric factor is due to the relatively small target area presented by an Fe centre in haemoglobin to a colliding O_2 molecule. In transition-state terminology the equivalent statement would be that the haemoglobin and O_2 molecules lose a considerable amount of rotational entropy on forming the activated complex, and clearly this is unlikely. The mere addition of O_2 should not effect the rotations of the haemoglobin molecule considered as a unit of M.W. 68,000. This is borne out by experiments in which the efficiency of physical-collision between H_2 and the Fe centre in haemoglobin was shown to be about normal¹⁷ (the collision efficiency was measured by the para-hydrogen conversion). In the formation of oxyhaemoglobin, however, we are concerned with chemical-collisions, i.e. collisions in which new bonds between Fe and O_2 are formed. The formation of these bonds will certainly influence the other bonds in the porphyrin and most likely also in the globin. If this leads to an increased "tightness" in the internal protein structure, or through an increase of charge on the protein lead to an increased force bonding the hydration shell, then negative ΔS^* values will be incurred. That is, the ΔS^* value is to be explained by internal changes in the protein structure, and we shall discuss such possible effects in more detail for the dissociation reaction later.

The results in Table I are for haemoglobin from sheep blood. Millikan¹⁸ has obtained very similar rates for human and horse blood, and we feel justified in comparing the data of Table I with equilibrium data on other bloods, in the next section.

The ΔS^* values indicate that the CO reactions behave more normally than those of O_2 . A further difference is revealed by the action of light, which will photochemically dissociate HbCO but not HbO_2 .¹⁹

No marked effect of salts was observed on any of the reaction rates. In the last section we shall suggest a hypothesis, which would certainly require a salt effect on the rate, but it is possible that such an effect would be difficult to detect in these extremely rapid reactions.

In conclusion, we must comment on our assumption of a transmission coefficient κ of 1, which of course effects the values of ΔS^* calculated. There is a change of electron spin in the reaction of Hb with O_2 (and also CO), since initially there are 4 unpaired electrons per haem in Hb , and O_2 has a multiplicity of 3 in its ground state, while HbO_2 has zero resultant electron spin.¹⁸ In such cases theory predicts the possibility of values of $\kappa < 1$, but up to date there is no certain experimental confirmation, i.e. all reactions whether or not involving a change in electron multiplicity may be assumed to have $\kappa = 1$. For reactions of proteins, the perturbation of the electronic levels due to the electrostatic field over the protein, arising from surface ionisation, will help to raise κ towards unity. For a balanced reaction the same value of κ is to be expected for forward and back reactions, if the small value of κ arises from a restricted electronic transition. So if the small A value of $\text{Hb} + \text{O}_2$ was really of the kind $\kappa < 1$, $\Delta S^* = 0$, and not $\kappa = 1$, $\Delta S^* = -30$, then, assuming a balanced reaction, the same value of κ should be taken for the HbO_2 dissociation, and an increased ΔS^* value of about 50-60 E.U. Our assumption of $\kappa = 1$, if wrong, will not invalidate the main points to be discussed in the penultimate section of this paper.

¹⁷ Eley, *Trans. Faraday Soc.*, 1940, 36, 500.

¹⁸ Millikan, *Proc. Roy. Soc. B*, 1936, 120, 366.

¹⁹ Pauling and Coryell, *Proc. Nat. Acad. Sci.*, 1936, 22, 159.

The Equilibrium Data.

The requisites of any simple balanced reaction are : -

(1) The equilibrium constant should equal the ratio of the forward velocity constant to the backward velocity constant.

(2) The overall entropy of the equilibrium should equal the difference between the entropies of activation of the forward and back reactions

i.e.

$$\Delta S = \Delta S^{\ddagger}_f - \Delta S^{\ddagger}_b.$$

(3) A similar relationship should apply to the energies of activation, viz.

$$\Delta H = E_f - E_b = \Delta H^{\ddagger}_f - \Delta H^{\ddagger}_b.$$

In their original paper Hartridge and Roughton¹⁰ established (1) for the $Hb + O_2$ reaction. This relationship is probably approximately true, although their determination of the equilibrium (pressure of O_2 vs. percentage saturation of Hb with O_2) appears to be in error to some extent. Using a spectroscopic method, they found the saturation curve to possess the simple hyperbolic character characteristic of Hitfner's theory. Later research by Roughton¹¹ has shown that dilute solutions of haemoglobin possess sigmoid saturation curves as do more concentrated solutions, and blood. Values of the equilibrium constant K determined by Hartridge and Roughton at about 50 % saturation should not be in great error, however. We have used Roughton's later determination of the dissociation curve, together with his values of ΔH ,¹¹ to estimate the ΔS values given in Table II. For this purpose we have calculated equilibrium constants K (and hence Gibbs function ΔG), assuming a simple equilibrium between 1 molecule of O_2 and 1 molecule of haemoglobin, giving the latter a molecular weight equal to its Fe-equivalent of 17,000 approximately. In this treatment we ignore the essential character of the reaction as involving intermediate compounds, as pointed out by Adair.¹² This theory will be referred to in subsequent discussion ; at this time we merely note that our treatment gives ΔS values sufficiently accurately for our purpose.

A reference to Tables I and II shows that conditions (2) and (3) are very far from holding (the discrepancy being well outside the experimental error), for haemoglobin and oxygen. For haemoglobin and carbon monoxide, on the other hand, conditions (2), and to a less extent (3), may be regarded as holding, within the rather large experimental error, the discrepancy being much less than in the first case. The value of ΔH quoted for CO is due to Adolph and Henderson,¹³ and their determination is not as accurate as Roughton's later work on $Hb + O_2$.¹¹ However, Adolph and Henderson's value of 7000 cal. for $Hb + O_2$ does not differ much from Roughton's values, and gives confidence in their value for CO.

Hartridge and Roughton¹ showed that the main burden for the effect of pH on the dissociation curve of HbO_2 (i.e. pO_2 vs. % HbO_2 equilibrium curve), is to be placed on the rate of dissociation rather than that of association. Since the curve for $HbCO$ is effected in an identical fashion by pH , we should expect a similar effect of pH on either or both of the reaction rates, and most probably on the dissociation rate. No such effect of pH on rate was observed in the CO case, and one can only conclude that an error has crept into these measurements.

The average value of ΔH for reaction (3) of 4000 cal. agrees well with the difference between reactions (1) and (2), both at pH 9.5, as it should do.

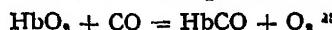
Data for haemocyanin (M.W. 0.5 - 5 \times 10⁶, a Cu-protein) and myoglobin (M.W. 17,000) are included as a matter of interest. No regular effect of molecular weight can be observed, ΔH for the largest molecule haemocyanin lying in between the values for haemoglobin and myoglobin.

¹⁰ Forbes and Roughton, *J. Physiol.*, 1931, 71, 229. Forbes, *ibid.*, p. 261.

¹¹ Roughton and others, *Biochem. J.*, 1936, 30, 2117.

¹² Adair, *Proc. Roy. Soc. A*, 1925, 109, 292 ; *J. Biol. Chem.*, 1925, 63, 529.

No simple regularities are revealed by the equilibrium data. It was hoped that the well-known relationship between the "span" (shift in the α band on changing HbO_2 to HbCO) and the equilibrium constant for



which holds over a range of haemoglobins (including myoglobin), might reveal the presence in all these haemoglobins of an excited energy state common to both HbO_2 and HbCO (*i.e.* at the same level of energy taking the ground state of HbCO as an arbitrary zero). A simple calculation soon showed that this was not so.

TABLE II.*

Equilibrium.	ΔH .	ΔS .	ϕ_H .	Notes.	Ref.
1. $\text{Hb} + \text{O}_2\text{aq.} \rightleftharpoons \text{HbO}_2$	-10,500	-12	9.5	Hb from ox blood — Hb from human blood	21
"	-6,550	-3	6.8		
"	-8,700	-	7.3		
2. $\text{Hb} + \text{COaq.} \rightleftharpoons \text{HbCO}$	-15,000	6	9.5	—	24
3. $\text{HbCO} + \text{O}_2\text{aq.} \rightleftharpoons \text{HbO}_2$	2,700	—	—	—	25
$\text{HbO}_2 + \text{COaq.} \rightleftharpoons \text{HbCO}$	6,000	—	—	—	26
	3,100	—	—	—	25
4. Haemocyanin	—	—	—	—	29
$\text{Hm} + \text{O}_2 \rightleftharpoons \text{HmO}_2$	-13,800	-23	7.4	—	29
5. Myoglobin	—	—	—	—	18
$\text{My} + \text{O}_2 \rightleftharpoons \text{MyO}_2$	-18,800	-38	7.4	—	18

* Values of ΔH and ΔS refer to the reaction of one mole of dissolved O_2 (or CO) with the haemoglobin or other pigment.

General Discussion, Assuming Transition-State Theory.

In certain ways the reaction $\text{Hb} + \text{CO}$ is similar to that of $\text{Hb} + \text{O}_2$. In each case the dissociation curve (equilibrium curve) is sigmoid, and effected in an identical fashion by ϕ_H . Recent work shows that HbCO and HbO_2 have identical values for the dissociation constants of their haem-linked acid groups.¹⁴ Other facts emphasise a dissimilarity. HbCO is sensitive to light, and therefore presumably has a different structure of electronic levels from HbO_2 . In the case of CO, the ΔS^* values for both forward and back reactions are more nearly normal than for O_2 , and furthermore the rate data checks up much better with the equilibrium data.

We cannot explain why the discrepancy between the CO and O_2 reactions is so marked. Certain suggestions may be made concerning the anomalies observed in the case of O_2 , but no reason can be given for the absence of similar anomalies in the case of CO. Since the data for O_2 is very well established, it certainly merits a detailed discussion.

The Theory of Successive Reactions.—Adair,²³ as a result of his determination of the M.W. of haemoglobin as 68,000 (so that haemoglobin therefore contained 4 Fe-porphyrin complexes, or haems), was able to give a rational explanation of the sigmoid dissociation curve of HbO_2 . His

²³ Anson, Barcroft, Mirsky and Oinuma, *Proc. Roy. Soc. B*, 1925, 97, 61.

²⁴ Hill and Wolverine, *ibid.*, 1936, 120, 489.

²⁵ Adolph and Henderson, *J. Biol. Chem.*, 1922, 50, 463.

²⁶ Schüller, *Biochem. Z.*, 1932, 255, 474.

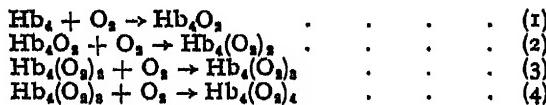
²⁷ Douglas, Haldane and Haldane, *J. Physiol.*, 1912, 44, 275.

²⁸ Brown and Hill, *Proc. Soc. B*, 1923, 94, 332.

²⁹ Millikan, *J. Physiol.*, 1933, 79, 158.

treatment was subsequently extended by Pauling,²⁰ Briefly, to saturate a haemoglobin molecule 4 O₂ molecules require to be added, and normally the addition will take place in 4 separate steps. Each O₂ added is to be regarded as increasing the affinity of the molecule for the next O₂ molecule to be added (*i.e.* there is an interaction between the oxy-heme groups in the haemoglobin molecule). Each successive step might have a different heat of reaction (as would be expected), and yet the overall heat of reaction per mole O₂ be independent of the ratio Hb/HbO₂, as experimentally observed (see Roughton²¹). Since the unimolecular and bimolecular constants appear to be independent of percentage saturation (*i.e.* they are true constants), it would appear that all 4 steps must have roughly the same value of the rate constants (p. 678¹⁰). Clearly, however, they may have different values of ΔS* and ΔH*. Series of reactions exist which possess very similar rates at the chosen temperature of measurement, but which possess varying values of the activation energy. In other words, the most likely interpretation of the results is that the activated complex for the forward reaction is different, and has a different energy and entropy, from that for the backward reaction, a suggestion which fits in plausibly with the intermediate compound hypothesis. For the CO case one must conclude that while the activated complexes for the forward and back reactions (*i.e.* overall measured reactions) may still be different, all the 4 steps have similar values for the energy and entropy of activation.

It is perhaps desirable to amplify the above statement, since it might be taken to imply a cyclical process, contradicting the principle of microscopic reversibility. The overall reaction, simply formulated by us as Hb + O₂ → HbO₂, in reality proceeds through intermediate steps involving compounds of the type Hb₄O₂, etc., which do not differ greatly from the final Hb₄(O₂)₄ in their stability, *viz.*



Our suggestion is that the overall association reaction, measured over 0-75 % saturation, is mainly determined by the activated complexes of the first, or first two steps. On the other hand, the dissociation process, measured mainly over 100 - 40 % saturation, will be mainly determined by the activated complexes of the last two steps. This is an explanation of a technical kind, only adopted after a search for a more physical explanation had failed. For example, it was suspected that the abnormality of the O₂ reaction, not shown by the CO reaction, might in fact reside in the great speed of the HbO₂ dissociation, which has a half-life of 0.02 sec. and is 10⁴ times more rapid than the HbCO dissociation. It was thought possible that the rate of energy fluctuation might be the determining factor here, but it will be shown in the concluding section that this explanation is an unlikely one. In the association reaction it is possible that the heat of reaction of step 1 might be retained within the molecule and not dissipated as heat, to be used to activate step 2, and so on. In this case a kind of intramolecular chain reaction would be set up, which would lead to discrepancies between true and apparent activation energy. In fact, indefinite speculation on this point is possible until the rate data for the individual steps have been established, and a reliable theory of the role played by energy exchanges in rapid chemical reactions has been established.

The Dissociation Rate of Oxyhaemoglobin.—The large values of ΔS* for the dissociation of HbO₂ are responsible mainly for the rapid rate of this reaction, and it is possible to indicate which is the most likely mechanism, out of the following probable ones.

²⁰ Pauling, *Proc. Nat. Acad. Sci.*, 1935, 21, 186.

(a) There is some experimental evidence that the hæm-protein fragments of M.W. 16,700 possess a certain degree of independence within the globular molecule of M.W. 68,000.²¹ If this is so, the formation of the activated-complex of oxyhaemoglobin might be associated with a loosening of the interaction between these fragments. Because of their high moment of inertia, a small increase in the rotational freedom of such a fragment will be accompanied by a large increase of entropy.

(b) The formation of the activated complex is accompanied by a decrease in the polarity of the co-ordination bonds to the hæm, with a subsequent decrease in the force holding water in the hydration shell in the neighbourhood, *cf.* point (c). This suggestion may be ruled out as unlikely right away, as the reverse effect is more likely to occur. Coryell and Pauling,¹⁹ on the basis of their magnetic measurements, have shown the co-ordination bonds of oxyhaemoglobin to be covalent, and of haemoglobin to be ionic.

(c) The formation of the activated-complex is accompanied by a decrease in total charge on the protein molecule, with a subsequent "loosening" of the hydration shell. The reverse effect, suggested by Stearn and Eyring, gave the first rational explanation of the large negative ΔS^* values encountered in the Menschutkin reaction.¹⁸ It is probably responsible for the large positive ΔS^* values found in bimolecular reactions between ions of opposite charge,²² and may be calculated to a first approximation by the simple electrostatic theory of Born.²³ A thorough treatment requires a detailed consideration of the hydration-shell.²⁴

(d) The formation of the activated-complex leads to a certain degree of disruption of the protein structure within the units M.W. 17,000 referred to under (a). This again might be due to a redistribution of internal polarity and the rupture of hydrogen-bonds.

We can rule out (a), by argument from myoglobin. This pigment has an M.W. of 17,000, and the hyperbolic dissociation curve that theory predicts for the primitive pigment, yet the rate of dissociation of oxymyoglobin is the same as that of oxyhaemoglobin.²⁵ We have not data to calculate the activation energy, but it is unlikely that this is less than for oxyhaemoglobin, and the equilibrium data would point to a larger value. ΔS^* for the myoglobin case is therefore probably at least that for haemoglobin, and yet for myoglobin the postulated effect (a) cannot arise, and it is therefore unlikely to be the operative factor in oxyhaemoglobin.

Mechanism (b) has been ruled out, leaving mechanisms (c) and (d) as the most likely, of those suggested. It is difficult to decide between these two; in (d) the effects of pH might be expected to be more important than those of salts. Hartridge and Roughton found no effect of salts on the dissociation rate, but it was not possible to conduct a thorough experimental test and they leave the point open. In most chemical reactions the activated-complex lies intermediate in properties between the reactant and the product. Such measurements as have been made find the isoelectric point for haemoglobin to be the same as for oxyhaemoglobin,²⁶ and this would suggest the difference in polarity between oxyhaemoglobin and its activated complex is small and that mechanism (c) is unlikely. So the balance of evidence lies in favour of (d), but further experimental work is required before a definite picture of the activated-complex in this reaction can be put forward.

The ΔS^* values suggest a connection between the properties of the protein and the bonds to the Fe in haemoglobin, which might properly be

²¹ Steinhardt, *J. Biol. Chem.*, 1938, 123, 543. A further reference has only been seen in *Chem. Abstracts*, Roche and Chonaisch, *Comptes Rendus*, 1939, 209, 1017.

²² Moelwyn-Hughes, *Proc. Roy. Soc. A*, 1936, 155, 308.

²³ Cf. ref. 6(b), p. 434.

²⁴ Eley and Evans, *Trans. Faraday Soc.*, 1938, 34, 1093.

²⁵ See Abramson, *Electrokinetic Phenomena*, pp. 158, 180. Chemical Catalogue Co.

described as a resonance effect. Both Warburg²⁶ and Michaelis²⁷ have indicated the importance of such a resonance, in lowering the activation energy for the reaction of substrate and prosthetic group in enzyme reactions. This lowering of activation energy by the protein would appear to be important in the haemoglobin case for the association reactions with O₂ and CO. In the *dissociation* reactions examined, however, its effect appears to be mainly on the "temperature-independent factor," or ΔS° term.

Conclusion.

There are two points to note. Firstly, in the dissociation of HbO₂, there is no reasonable possibility of a chain reaction. Therefore, in enzyme reactions very large A values are not necessarily to be associated with a chain mechanism. Unless it has been proved otherwise, they may also be due to the effects associated with the internal freedom, or hydration, of the protein that have been discussed above.

Secondly, it might be asked if the peculiar behaviour of the HbO₂ dissociation is not due to the application of transition-state theory to a case where it should not be applied; namely to a case where the rate is governed by the redistribution of the true activation energy E_t, contained in a number (s) of degrees of freedom of vibration. This point is discussed in detail for the general case in a forthcoming publication. In the present case it appears very unlikely, for the following reasons. Where the rate is governed by a distribution of energy, the appropriate equation is

$$k = \lambda \left(\frac{E_t}{RT} \right)^s \frac{1}{(s-1)!} e^{-E_t/RT}$$

where λ is the probability of the energy accumulating in the particular bond requiring it for reaction, and is usually taken as about 10¹⁸ sec.⁻¹. The experimental activation energy is then

$$E_{\text{exp}} = E_t - (s-1)RT.$$

Therefore the true activation energy will be *greater* than 25,000 cal., and this serves only to *increase* the observed discrepancy with the overall-heat of reaction. Further, ϕII has a marked effect on the A factor, but it seems rather a strain on the theory to postulate an effect of ϕII on λ, or even on s.

It is a pleasure to acknowledge discussions with Professor E. K. Rideal and Professor M. Polanyi on the topic of this paper.

Summary.

The data of Hartridge and Roughton have been employed to calculate values of the energy and entropy of activation of the reactions of haemoglobin with O₂ and CO, in aqueous solution. These values have been discussed with particular reference to the energies and entropies of the related equilibria, with the following conclusions.

The reaction with CO appears to be relatively normal by the standards of chemical kinetics.

The reaction with O₂ is distinctly abnormal, the difference between the activation energies between the forward and back reactions being widely different from the heat of reaction. It is concluded that the activated complexes for the observed forward and back reactions are different, belonging to different steps in the chain of successive reactions postulated by Adair.

²⁶ Warburg, *Ergab. Enzymforschung*, 1938, 7, 210.

²⁷ Michaelis, *Cold Spring Harbour Symposium*, 1939, 7, 33.

The association reactions are marked by their low value of the activation energy, but the dissociation reaction of HbO_2 is marked by its high value of the entropy of activation. It is exceedingly unlikely that this is an unreal value, due to a chain reaction, nor does it appear that consideration of the rate of energy-distribution in the molecule is important. It is most probably due to a loosening of the internal structure of the protein on forming the activated complex.

REVIEWS OF BOOKS

Temperature Control. By A. J. ANSLEY. Pp. viii + 126. London: Chapman and Hall, Ltd., 1942. 13s. 6d.

The control of temperature is a problem which, in one form or another, arises in most laboratory or technical operations. Requirements are extremely varied: thus it may suffice to maintain a system within a few degrees of a given temperature in one case, while in another a control within 0.1° or less is essential. It is not surprising, therefore, that the most varied methods have been employed, though comparatively few are mentioned in standard books on laboratory technique. The author of this admirable little book describes many of these methods of control applicable in temperature ranges between 0° and 1500° . They are grouped in successive chapters according to the physical effects forming the basis of the regulating device, and include liquid expansion controls, vapour baths and vapour pressure methods, metal expansion controls, gas expansion controls, methods based on the change of resistance with temperature, temperature controls using the photo-electric effect and thermo-electric current control. The three final chapters deal with temperature control as applied to scientific instruments (refractometers, spectrographs, microscopes and piezo-electric oscillators), with liquid baths and with air baths. Appendixes have also been included on relays, galvanometers, the Wade and Merriman pressure manostat and thermal constants.

The choice of the method most suited for any particular problem can safely be based on the details given here. The author has appreciated the limitations of some laboratories and has included descriptions of the simplest devices as well as of much more elaborate regulators, some of which are commercial articles. In all, eighty-one diagrams are given, together with a large number of references to original papers. Many minor experimental points, upon the proper appreciation of which the success of a piece of apparatus so often depends, are also fully explained. This is certainly a book which will be most valuable in research laboratories and in industry. Not its least merit is that, while it is highly informative, it does not present the subject in a final form. Instead it offers every encouragement for improvisation and for the improvement of existing methods.

H. J. E.

A Treatise on Physical Chemistry. Edited by H. S. TAYLOR and S. GLASSSTONE. Vol. I: Atomistics and Thermodynamics. (Van Nostrand; Macmillan. Pp. vii x 670. 42s.)

An extract from the definition of chemistry given in the O.E.D. is Chemistry Forms *chymistrie, chmistry, chymstry, chemistry*: "the art and practice of the chemist"; at first probably contemptuous, cf. palmistry, sophistry, casuistry, etc.

That branch of physical science and research which deals with the several elementary substances, or forms of matter, of which all bodies are composed, the laws that regulate the combination of these elements in the formation of compound bodies, and the various phenomena that accompany their exposure to diverse physical conditions.

Under physical will be found "In special phrases and collocations . . . Physical chemistry, that branch of chemistry which deals with the structure of molecules.

If one accepts the above statements, then Volume I of *A Treatise on Physical Chemistry* has little if anything to do with physical chemistry. Volume I consists of four chapters, each of which is a monograph on a special topic. Four further volumes on the same plan are in preparation, "to follow at intervals of several months, presenting in succession States of Matter, Chemical Equilibrium, Chemical Kinetics and Molecular Structure." There is an impressive amount of material in Volume I, and extensive quotations have been made from articles and books of recognised authority. The four chapters will now be discussed separately.

Chapter I. The atomic concept of matter, by H. S. Taylor. This is an essay mainly about nuclei. Methods of measuring the fundamental constants, e , h and m , or combinations thereof, are described and the results given. Then follow the mass spectrograph and the nuclear masses. Next come twenty excellent pages on the separation of isotopes (by diffusion processes, electrolysis and chemical exchange). The remaining forty pages are concerned with nuclear processes, and include comprehensive tables of stable isotopes and their abundances, and induced radioactivities (taken from Livingood and Seaborg's article, *Rev. Mod. Physics*, 1940, 12, 30).

Chapter II. Quantum theory of atomic spectra and atomic structure, by S. Dushman. This is an excellent chapter. It is a careful account of the experimental facts on which non-relativistic quantum theory rests, and a simple treatment of the theory. The style is reminiscent of Sommerfeld's *Atombau*, or Ruark and Urey's *Quantum Mechanics*. To those seeking a knowledge of quantum mechanics with a view to application in photochemistry, chemical kinetics and "chemical physics" generally, it would be difficult to recommend a shorter or more readable article covering the same ground.

Chapter III. The first and second law of thermodynamics, by H. S. Taylor. This is an orthodox account of the first and second laws, supplemented by tables of useful data, such as the heat content of gaseous hydrocarbons at N.T.P., and Joule-Thomson coefficients, and by the standard partition functions for rotational and vibrational motion of molecules.

No mention is made of Carathéodory's work. Surely it is time that at least a summary should appear in text-books on thermodynamics.

Chapter IV. The third law of thermodynamics and statistical mechanics, by J. G. Aston. This article is mainly concerned with thermodynamic properties of crystals near the absolute zero. Many of the general principles of statistical mechanics are discussed (μ method). The heat capacity of vibrators, rigid rotators and tops with internal rotators are worked out and experimental results quoted in illustration. Much of the algebra, often lengthy, is given chapter and verse (a good point this; provided it is done well enough, as appears to be the case here). The third law, stated in the first ten pages, is then used to evaluate the equilibrium constants of chemical reactions involving crystalline solids. This leads on to a discussion of energy levels and heat capacities of crystalline solids and to an account of paramagnetic cooling methods. Throughout the article, full quotations are made of the experimental results. Finally, there is an appendix giving tables of useful thermodynamic functions of the harmonic oscillator and the internal rotator.

Finally, a few comments on the book. If one is familiar with some special topic and wished to check some small point, one would not as a rule go to this book. Instead one would know where a fuller account was to be found in a specialised book. If, on the other hand, one wished to get a quick survey of a field, with full references to more exhaustive accounts, Vol. I is the sort of book one would try. Sometimes, one would be lucky and get the whole thing *in extenso*; more often, it would be mentioned briefly and references given to more specialised accounts. In a few words, then, Taylor and Glasstone have produced the first volume of a series that promises to be of the type they desired; Vol. I will be invaluable in any centre where research on atoms or molecules is in progress.

The printing, binding, diagrams and paper are all of the highest quality. The price is reasonable.

W. G. P.

Volumetric Analysis. Volume I. By I. M. KOLTHOFF and V. A. STENGER. (Interscience Publishers, Inc., New York. 1942. \$4.50. Pp. xv and 309.)

Additions to the literature of quantitative analysis which candidly discuss the merits, errors and field of usefulness of well-studied methods or which lay emphasis on the principles of analytical procedure in general will always be welcome. The present volume deals thoroughly with the theory and errors of volumetric analysis but, while many determinations are mentioned, the manipulative details are deferred to the second volume.

The fourteen years which have passed since the appearance of the first edition in English have seen a great many developments, which have necessitated a very considerable extension and revision. The latter might advantageously have been more rigorous; the atmosphere of 1928 still lingers, for example, in the chapter entitled "Reaction Velocity."

Errors are neither numerous nor serious. Exception must, however, be taken to the confusing use (p. 155) of k as a symbol for concentration.

There is a vast amount of valuable information and experience collected in this volume and it can be recommended to all those interested in analysis as a means or an end.

D. W. G. S.

Hydrogen Ions. Their Determination and Importance in Pure and Industrial Chemistry. By H. T. S. BRITTON. Third Edition in two volumes. (Chapman & Hall. London. 440 and 464 pp. Each volume, 36s.)

In its third edition, this well-known monograph has undergone a welcome change. In place of the inconvenient bulk of the second edition it now appears in two manageable volumes which can be comfortably held in one hand. What may be termed the academic section is contained mainly in the first volume, while the second is devoted to the technical applications together with some matter of more academic character which has overflowed from the first.

In spite of war difficulties, the work has been considerably extended and brought up to date. Old chapters have been subdivided and several new chapters have been included. In particular, Redox Potentials, a noteworthy omission from the previous editions, are now treated in a special chapter. In consequence the number of pages has been increased by some 50 per cent.

Many of the diagrams have been redrawn with gain in their clarity. The printing and binding are fully up to pre-war quality.

D. W. G. S.

Synthetic Resins and Allied Plastics. Edited by R. S. MORRELL. Second Edition. (Oxford University Press, London : Humphrey Milford, 1943.) Pp. xii + 580. 35s.

Much of the matter in this second edition has been rewritten and the whole book has been carefully revised. The general lay-out is similar to that of the first edition. The various chapters are given under the authority of experts ; for instance, Dr. Yarsley writes a chapter on Protein and Cellulosic Plastics, Dr. Hill on the Vinyl and Acrylic Acid Resins and Mr. Bevan on the Alkyd Resins. The chapter on the Causes of Resinification has been very considerably rewritten by Dr. Morrell under the title, "The Problems of Resinification," and now appears as two separate chapters, the first of which might have been given the sub-heading "General" and the second "Specific."

The book brings the subject well up to date. It necessarily includes a great deal of matter which was not present in the 1937 edition and there are now 580 pages instead of 417. The blemishes which the reviewer found in the first edition have been removed. This will be found to be a valuable addition to the library of all who are interested in resins and plastics.

MAGNETOCHEMICAL INVESTIGATIONS.

PART I. INTRODUCTION AND EXPERIMENTAL TECHNIQUE.

BY W. ROGIE ANGUS AND W. K. HILL.

Received 1st February, 1943.

Not only did the exhaustive and systematic investigations of Pascal¹ from 1908 to 1925 establish the additivity of magnetic susceptibility but they have, particularly in regard to organic compounds, been instrumental in strengthening the relation of magnetism to chemistry and molecular structure. Since susceptibilities are additive it follows that every atom and ion can be assigned a definite value. Pascal, from a study of numerous diamagnetic compounds of widely different molecular types, deduced values for a large number of atoms and groups. It must be emphasised, however, that these values are not for free atoms but for atoms combined in a molecule. Thus, a large number of attempts have subsequently been made to obtain values for free atoms and for ions; and two main lines of approach to the problem have been used—evaluation from experimental data and calculation from theory. But the various methods do not lead to concordant values even for the simplest types of atoms, those having an inert-gas configuration.²

The values for atoms deduced by Pascal require to be corrected because he used the value of -0.75^* for water, whereas the accepted value now is -0.72 . These corrected atomic susceptibilities, used additively, yield values for molecular susceptibilities in fairly accurate agreement with experimental data; but a critical examination reveals inconsistencies.

The results now reported represent the initial measurements in a big programme commenced in 1938 and now temporarily suspended. It is the purpose of these investigations to ascertain whether the inconsistencies already referred to are real or not. A probable cause is the variety of experimental techniques which have been used by the different workers in this field. Much of the published work gives no details of the technique of the measurements or the methods of purifying the substances examined. In this paper a modified Gouy method and its calibration will be briefly described. The necessity for rigorous purification of substances cannot be too strongly stressed; even traces of impurity may substantially alter the value of the susceptibility. But errors may arise in spite of the utmost care in purification unless the investigator always follows the same technique of measurement.

Experimental Arrangement.

(a) Susceptibility Tube.—This was a flat-bottomed glass tube having two solid glass side-arms, and fitted with a ground glass stopper to prevent contamination and, in the case of liquids, evaporation.

(b) Suspension System.—The tube was suspended from one arm of a sensitive chemical balance by means of an enamelled copper wire and stirrup, into which the side arms of the tube were placed, so that it hung

¹ (a) *Compt. rend.*, 1909, 149, 342; (b) *Ann. Chim.*, 1910, 19, 5; (c) *Bull. Soc. Chim.*, 1911, 9, 79; (d) *ibid.*, 1911, 9, 177; (e) *Compt. rend.*, 1925, 180, 1596.

² Angus, *Ann. Rep.*, 1941, 38, 27.

* Susceptibility values have been multiplied by 10^8 .

at rest with its lower end at the centre of the gap between the pole pieces of the electromagnet. An ordinary balance pan hung from the other end of the balance beam. Weighings were made by the method of swings using N.P.L. certified weights and, to enhance the accuracy of weighing, the suspension system and the susceptibility tube were enclosed in a draught-proof box, the front of which could be removed so as to permit of adjustment of the susceptibility tube.

(c) Electromagnet.—Constructional details of the electromagnet are shown in Fig. 1 and require only brief amplification. The apparatus was completely made in this department. The magnet coils each consist of 1,200 yards of No. 18 s.w.g. double cotton-covered copper wire wound on an insulating cylinder, each layer being painted with shellac varnish.

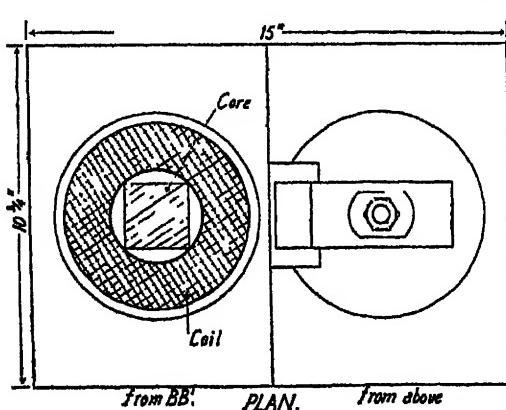


FIG. 1.

into the magnet cores. The whole magnet was fixed rigidly to a thick wooden base by 4-inch bolts which screwed into the bottom ends of the cores. The coils heated up slightly when the current was switched on and to obviate alteration of the temperature of the gap—and thereby of the specimen being examined— asbestos paper was placed between the brass plates and the pole pieces. The current supply was 230 v. D.C. Constancy of the current supplied was maintained by a circuit consisting of a moving coil ammeter with a linear scale and a slide wire regulating resistance of 73 ohms, 3·3 amp. continuous rating. In order to prevent the excessive rise of voltage, due to discharge of the magnet coils when the current is switched off, a secondary circuit was incorporated. It consisted of a 500-ohm discharge resistance, made by winding 40 yards of No. 30 s.w.g. bare nichrome resistance wire, and a control switch arranged to connect the resistance across the magnet coils before the current is interrupted.

Calibration of Apparatus.

(a) General Considerations.

The theory of the Gouy method is sufficiently well known that it need not be given here: the expression for the susceptibility, χ , simplifies to $\chi = (c + \alpha F)w$, where $c = \kappa_1 A$ and $\alpha = 2l/(H_1^2 - H_2^2)$; κ_1 = volume susceptibility of air; F = force acting along a cylinder of material of length l , weight, w , and internal cross-sectional area, A .

The constancy of α depends on the constancy of $(H_1^2 - H_2^2)$ and finally on H_1 and H_2 , the field strengths at the bottom and top of the column.

H_1 should be constant over several mm. on each side of the centre of the gap and the top of the column of the specimen must be at such a distance

The completed coils were baked for several hours before assembling and gave a resistance of 150 ohms in series. The tops and bottoms of the bobbins were circular $\frac{3}{8}$ inch brass plates. The magnet cores and pole-pieces were made from 2-inch square Low Moor soft iron and were connected by $\frac{1}{4}$ -inch bolts. These bolts passed through elongated slots in the pole-pieces, thus enabling the gap to be adjusted to any desired width, and were screwed

from the centre of the gap that H_1^s is negligible compared with H_1^a . The direct measurement of H_1 and H_2 by a fluxmeter gives values which are suspect because fluxmeter deflections cannot be read with high accuracy. A more accurate method of determining α is by reference to certain compounds which are readily obtained pure and for which accurate magnetic data are available. Further factors which demand the utmost care are the height of the column, filling the tube exactly to the appropriate graduation mark, and close and uniform packing when solids are being examined.

(b) Variation in flux density with current was determined, using an ebonite search coil in a 1 cm. pole-piece gap with its leads connected to a Grasset fluxmeter, over the current range of 0.94 to 1.30 amp. and from the data (Table I) it will be seen that an approximately linear relationship exists between current and field strengths and that the saturation point of the cores lies beyond the available maximum current supply; θ is the mean of approximately 8 fluxmeter deflections and represents a field strength, H , of $15,000\theta/nA$ gauss (n = no. of turns; A = area of coil).

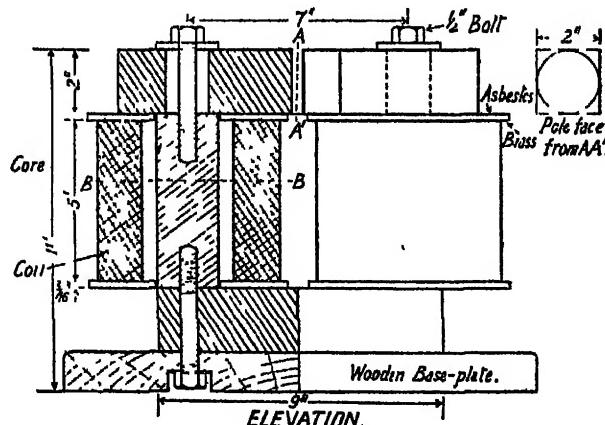


FIG. 2.

TABLE I

Amps.	θ .	H (gauss.).	Amps.	θ .	H (gauss.).
0.94	79.11	6240	1.10	81.62	6450
0.96	79.04	6240	1.12	82.12	6490
0.98	79.59	6290	1.14	82.70	6530
1.00	80.20	6330	1.18	83.20	6570
1.02	80.48	6360	1.20	83.48	6600
1.05	80.73	6380	1.24	84.41	6670
1.06	81.24	6420	1.30	85.21	6730

It was decided to use a field strength of 6600 gauss (1.2 amp.) in subsequent measurements.

(c) Variation in flux density with distance from the centre of the gap was determined in two ways: (i) by a search coil, the position of which could be altered vertically, (ii) a column of copper sulphate.

The variation of θ , fluxmeter deflections, with distance of the coil from the centre of the gap is given in Table II; the negative sign indicates distances below the centre of the gap.

These data indicate the symmetrical diminution in field strength as the distance from the centre of the gap increases and that the field strength at 6 cm. or more from the centre is practically negligible compared with that at the centre. To check them a susceptibility tube with a 10 cm.

TABLE II

d (cm.)	+6.0	+5.0	+4.0	+3.0	+2.5	+2.0	+1.5
θ	8.5	11.0	12.6	17.9	105.4	113.5	113.6
d (cm.)	1.0	1.5	centre	-2.0	-1.0	-0.0	
θ	113.3	113.2	113.4	110.8	109.2	8.7	

column of finely-ground, recrystallised AnalaR CuSO₄.5H₂O was suspended by a movable copper stirrup with the bottom of the tube in the centre of the gap. The tube and contents were weighed; then with a current of 1.2 amp. passing through the coils it was re-weighed. The difference in the two weighings gives the pull F due to the magnetic field. The results, which are tabulated in Table III, are in very good agreement with the search coil data but refer only to heights above the centre of the gap.

TABLE III

d (cm.),	Weight (gm.) with Current—		F (gm.).	$F^{\frac{1}{2}}$ (gm.).
	Off.	On.		
centre	14.8291	14.8789	0.0498	0.2231
0.35	14.8291	14.8785	0.0494	0.2223
0.56	14.8291	14.8783	0.0492	0.2218
0.74	14.8291	14.8781	0.0490	0.2214
1.15	14.8291	14.8772	0.0481	0.2189
1.55	14.8291	14.8765	0.0474	0.2177
1.94	14.8291	14.8760	0.0469	0.2166
2.79	14.8291	14.8572	0.0281	0.1677
3.30	14.8291	14.8371	0.0080	0.0654
4.05	14.8291	14.8305	0.0014	0.0374
4.72	14.8291	14.8292	0.0001	0.0100

It is clear, therefore, that only a negligible error will be introduced if columns longer than 6 cm. are used. Accordingly, susceptibility tubes were etched at 6 and 6.5 cm. and the longer column was used whenever sufficient material was available.

(d) Determination of C.—The volume susceptibility of air, κ_0 , is 0.029. Thus the evaluation of C ($= \kappa_0 A l / I$), since the definite lengths of column to be used in making measurements had been decided upon as 6.0 and 6.5 cm., consisted in measuring A , the internal cross-sectional area of the susceptibility tube. The average value for A was found to be 0.2026 sq. cm. and C is, therefore, 0.03647 for the 6 cm. column and 0.03951 for the 6.5 cm. column.

(e) Determination of α .—To evaluate α the values of I and $(H_1^a - H_2^a)$ must be known accurately. It was considered advisable to use a relative method in which α was measured by reference to chemical substances, readily obtained pure and having accurately-known magnetic susceptibilities by making a "susceptibility" measurement on finely-ground powders. F was determined and hence α could be calculated.

By this procedure values of α for 6 cm. and 6.5 cm. columns of specially purified salts were obtained (Table IV); the values of α were obtained from the data of Jackson³ and Sugden.⁴

³ Phil. Trans., A, 1924, 224, 1.

⁴ J.C.S., 1932, 161.

TABLE IV

Compound.	$\theta^\circ \text{ C.}$	χ .	$w \text{ (gm.)}$.	$F \text{ (mg.)}$.	α .
6 cm. column.					
NiSO ₄ · (NH ₄) ₂ SO ₄ , 6H ₂ O ³	18·4	10·485	1·80734	78·113	0·2422
FeSO ₄ · (NH ₄) ₂ SO ₄ , 6H ₂ O ³	16·5	32·055	0·78560	103·800	0·2479
FeSO ₄ , 7H ₂ O ³	18·4	32·446	0·77008	101·347	0·2462
FeSO ₄ , 7H ₂ O ³	19·8	41·008	0·77517	129·235	0·2458
FeSO ₄ , 7H ₂ O ³	21·0	40·840	0·75810	127·500	0·2471
CuSO ₄ , 5H ₂ O ⁴	18·0	6·020	1·98328	48·058	0·2477
CuSO ₄ , 5H ₂ O ⁴	18·0	6·020	1·95310	47·500	0·2497
6·5 cm. column.					
NiSO ₄ · (NH ₄) ₂ SO ₄ , 6H ₂ O	18·8	10·472	1·96309	78·349	0·2618
	25·0	10·270	1·87020	73·400	0·2610
FeSO ₄ · (NH ₄) ₂ SO ₄ , 6H ₂ O	18·0	32·400	0·84800	101·200	0·2609
FeSO ₄ , 7H ₂ O	19·6	32·314	0·83183	100·728	0·2665
FeSO ₄ , 7H ₂ O	18·2	41·232	0·82425	127·991	0·2653
	22·5	40·630	0·82850	127·310	0·2655
CuSO ₄ , 5H ₂ O	17·1	5·912	2·14675	48·219	0·2623
	19·0	6·140	2·11300	47·700	0·2701

The average values thus obtained were :

6 cm. column : $\alpha = 0·247 \pm 0·001$; 6·5 cm. column : $\alpha = 0·265 \pm 0·001$.

These data, of course, refer to only one tube; for every tube similar data must be obtained.

To check these values, and in order to have a convenient method of standardising susceptibility tubes, a solution of nickel chloride (21·650 g. Ni per litre) was prepared. The susceptibility of this solution was then determined using the appropriate value of α , the analytical data, and the equation $\chi = c_s \chi_s - (1 - c_s) \chi_w$, where c_s is the weight of NiCl₂ in the solution \div total weight of solution, χ_w is the mass susceptibility of the conductivity water ($= -0·732$), and χ and χ_s are, respectively, the mass susceptibilities of the solution and NiCl₂. This yielded an average value of 4478 ± 9 which is not only in excellent agreement with the recorded

TABLE V

T° .	$w \text{ (gm.)}$.	$F \text{ (mg.)}$.	χ_s .		$4\chi_s$.
			Experimental.	Theoretical.	
290·0	1·4877	22·719	4·095	4·088	+ 0·007
290·5	1·4877	22·662	4·085	4·080	+ 0·005
290·6	1·4867	22·606	4·077	4·078	- 0·001
291·8	1·4877	22·507	4·057	4·059	- 0·002
292·8	1·4867	22·422	4·044	4·043	+ 0·001
293·0	1·4878	22·390	4·036	4·040	- 0·004
293·7	1·4865	22·324	4·028	4·029	- 0·001
294·1	1·4865	22·294	4·021	4·022	- 0·001
294·5	1·4867	22·288	4·021	4·017	+ 0·004
294·8	1·4867	22·267	4·017	4·012	+ 0·005

³ Proc. Acad. Sci. Amsterdam, 1915, 18, 246.

⁴ Physic. Rev., 1921, 17, 697.

⁵ Proc. Roy. Soc., A, 1939, 173, 313.

values of Weiss and Bruns (4448),⁵ Brandt (4423),⁶ and Nettleton and Sugden (4468)⁷ but affords excellent confirmation of the values of α deduced (Table IV). Periodically α was redetermined, using NiCl_3 , in order to ensure accuracy and self-consistency of results.

A further check was rendered possible through the kindness of Professor S. Sugden, F.R.S., who gave us a sample of a concentrated solution of NiCl_3 which had been analysed and examined magnetically by him at University College, London. Since NiCl_3 obeys the law

$$\chi_s = 10030x/T - (1-x)\chi_w$$

where x = weight of NiCl_3 per g. of solution, and χ_w = susceptibility of water, χ_s = susceptibility of 1 g. of solution at T° Abs. can be calculated. The values thus derived for χ_s are given in Table V in the column headed "Theoretical." Also included in this Table are the values we obtained by measuring χ_s at different temperatures using the values of α reported above.

These various data show very clearly the accuracy of the standardisation of the apparatus and the consistency of the experimental technique.

Summary.

A modified Gouy method for measuring magnetic susceptibilities is described. The electromagnet gives a field of 6,600 gauss at 1.2 amp. for a pole-piece gap of 1 cm. Calibration of the apparatus is discussed and the need for making measurements by a standardised technique is stressed.

It is a great pleasure to express our thanks to Professor W. E. Williams, Head of the Department of Applied Electricity, for advice regarding the design of the electro-magnet and for the loan of the Grassot fluxmeter; to Mr. M. W. Humphrey Davies, Lecturer in Applied Electricity, for preparing detailed plans of the electromagnet and supervising its construction; to Mr. T. R. Jacobs, mechanic in this Department, for the painstaking and skilful manner in which he constructed the electromagnet; to the Low Moor Steel Co. Ltd., for the gift of the soft iron from which the cores and pole-pieces were made; to Professor S. Sugden, F.R.S., for helpful advice and discussion.

PART II. THE DIAMAGNETIC SUSCEPTIBILITY OF THE $>\text{CH}_3$ GROUP.

From the diamagnetic susceptibilities of a large number of compounds constituting different homologous series Pascal obtained a mean value of -11.86 for the susceptibility of the $>\text{CH}_3$ group. This was obtained by subtracting the molecular susceptibility of any compound from that of its next higher homologue and the method implied that all homologous series were built up by the successive addition of $>\text{CH}_3$ groups. Consequently, the same value should be obtained from all series, irrespective of their chemical properties. This view is, indeed, maintained by Bhatnagar and Mitra,¹ who critically examined Pascal's values and corrected them to the standard value of $\chi_{\text{H}_2\text{O}}$, i.e., from $\chi_{\text{H}_2\text{O}} = -0.75$ to $\chi_{\text{H}_2\text{O}} = -0.72$. As a result they concluded that the (numerically) maximum average value of χ_{CH_3} is -11.68 . Pascal, however, obtained an average value for χ_{CH_3} for some series which was

¹ Bhatnagar and Mitra, *J. Indian Chem. Soc.*, 1936, 13, 329.

considerably different from his mean value, e.g., for nitrocompounds he gives — 11.42.

Various attempts have been made to re-examine homologous series with a view to determining the $>\text{CH}_2$ increment and its variation with the nature of the terminal group of the hydrocarbon chain.

All these attempts suffer from the defect that too few substances have been examined to warrant far-reaching conclusions.

Cabrera and Fahlenbrach¹ examined 7 *normal* alcohols; Woodbridge²—acetic acid and 5 *normal* acetates from methyl to amyl; Gray and Cruickshank³—3 homologous series, organic nitrites, nitrates, and nitro-compounds (in all, 8 compounds were examined); Bhatnagar, Mitra and Tuli⁴—aliphatic alcohols, monocarboxylic acids, and esters (15 in all), and 5 benzene hydrocarbons; Farquharson and Sastri⁵—5 *normal* monocarboxylic acids. Thus, at the commencement of the investigations the question was unanswered and confused as the results in Table I show.

The contemplated programme, temporarily discontinued, included a systematic re-investigation of a large number of homologous series under carefully controlled and standardised conditions.

TABLE I

Author.	χ_{CH_2} .
Pascal (corrected) . . .	-11.42 to -11.86
Cabrera and Fahlenbrach . . .	-11.48
Woodbridge . . .	-11.67
Gray and Cruickshank . . .	-11.87
Bhatnagar, Mitra and Tuli . . .	-11.36
Farquharson and Sastri . . .	-11.64
This paper (Pascal's method)	-11.68 + 0.02
This paper (Farquharson and Sastri's method) . . .	-11.69 + 0.003

TABLE II

Sample.	w (grams).	F (mg.).	χ_s	Δ .
A . .	{ 1.0385 1.0385 1.0384	— 2.698 — 2.696 — 2.691	0.663 0.663 0.662	+ 0.003 + 0.003 + 0.002
	{ 1.0398 1.0406 1.0405 1.0404	— 2.691 — 2.685 — 2.691 — 2.689	0.661 0.660 0.661 0.660	+ 0.001 0.000 + 0.001 0.000
B . .	1.0385	— 2.672	0.657	- 0.003
	{ 1.0383 1.0383 1.0381	— 2.694 — 2.663 — 2.666	0.662 0.655 0.655	+ 0.002 - 0.005 - 0.005
	{ 1.0389 1.0388	— 2.698 — 2.676	0.663 0.658	+ 0.003 - 0.002

Experimental.

Purification of substances was carried out by standard methods and until constancy in the value of the mass susceptibility was obtained.

Measurement of Susceptibility.— Using the apparatus described in Part I the value of χ , was determined at least six times for each substance. The data for methyl alcohol in Table II illustrate the method and the accuracy. (Sample B was obtained

from sample A by redistillation; readings obtained with the same filling of the tube are bracketed; w, F, and χ_s have the same significance as in Part I; Δ is the deviation from the mean value of χ_s).

¹ Cabrera and Fahlenbrach, *Z. Physik*, 1935, 85, 568.

² Woodbridge, *Physic. Rev.*, 1935, 48, 672.

³ Gray and Cruickshank, *Trans. Faraday Soc.*, 1935, 31, 1491.

⁴ Bhatnagar, Mitra and Tuli, *Phil. Mag.*, 1934, 18, 449.

⁵ Farquharson and Sastri, *Trans. Faraday Soc.*, 1937, 33, 1472.

MAGNETOCHEMICAL INVESTIGATIONS

TABLE III

Series.	B.P. (°C/mm.).	P_4^{25} .	n_D^{25}	$-X_H^L$	$-X_M^L$	No. of Measurements.	Recorded Val. of $-X_M^L$
1. Alcohols:							
Methyl	64.748	0.7865	1.3276	0.660 ₈	21.15	13	21.6 ^a ; 21.42 ^b ;
EthyI	77.7/74.8	0.7858	1.3595	0.777 ₅	33.05	10	21.27 ^c ; 33.71 ^c
<i>n</i> -Propyl	96.8/74.8	0.7999	1.3834	0.739 ₈	41.44	7	44.92 ^d
<i>iso</i> -Propyl	80.8-/63	0.7969	1.3756	0.758 ₉	45.68	9	46.0 ^e
<i>n</i> -Butyl	116.7/74.8	0.8063	1.3976	0.757 ₈	56.15	8	56.32 ^f ; 55.26 ^g
<i>iso</i> -Butyl	107.2-/64	0.7983	1.3932	0.771 ₈	57.21	7	57.9 ^g
<i>sec</i> -Butyl	99.5-/61	0.8015	1.3959	0.773 ₆	57.30	10	56.0 ^g
<i>tert</i> -Butyl	81.6-/81-97/75 ⁱ	—	—	0.774 ₇	57.42	10	—
<i>iso</i> -Amyl	131.3/76.3	—	1.4050	0.782 ₅	68.96	9	68.57 ¹⁶
<i>neopentyl</i>	—	—	1.4059	0.783 ₄	69.06	10	—
2. Acids:							
Acetic \ddagger	(f.p.) 15.9	—	—	0.528 ₈ *	31.72	6	31.4 ^h ; 31.63 ⁱ ; 31.8 ¹⁰ ; 31.9 ¹¹ ,
Propionic	140.9-141.3/76 ^j	0.9940 [†]	1.3871 [†]	0.585 ₃	43.36	7	32.0 ₁₁ ; 32.1 ₂ ,
<i>n</i> -Butyric	162.2-162.5/76 ^j	0.9551 [†]	1.3950	0.626 ₈	55.20	11	43.8 ₁₁ ; 55.07 ^g ; 55.39 ¹³ ;
<i>iso</i> -Butyric	153.1-153.3/76 ^j	0.9442 [†]	1.3192	0.636 ₈	56.06	8	55.48 ¹⁴ ; 55.70 ¹⁵
<i>n</i> -Caprylic	203.0-203.5/75 ^j	0.9225	1.4154	0.676 ₈	78.55	10	78.14 ^g
3. Aliphatic Esters:							
(a) Formates—							
<i>n</i> -Butyl	106.1/75.4	0.8864	1.3871	0.641 ₈	65.83	10	—
<i>iso</i> -Butyl	97.1/74.5	0.8772	1.3835	0.654 ₈	66.79	10	—
<i>iso</i> -Amyl	122.7/74.7	0.8751	1.3960	0.674 ₈	78.38	9	—

(b) Acetates—											
Methyl	.	56.5/753	0.9262	1.3594	0.571 ₃	42.37	12	42.23 ³	53.0 ₃ ³	54.3 ³	
Ethyl	.	76.4/753	0.9843	1.3703	0.611 ₀	54.00	8	53.75 ³	55.75 ³	55.94 ³	
* n-Propyl	.	101.4/760	0.9811	1.3821	0.645 ₃	65.91	9	—	—	—	
* iso-Propyl	.	86.1-88.1/753	0.8629	1.3748	0.656 ₄	67.04	8	—	—	—	
n-Butyl	.	125.5/753	0.8749	1.3922	0.666 ₃	77.47	18	77.00 ³	—	—	
iso-Butyl	.	116.8/770	0.8645	1.3877	0.670 ₀	78.52	10	79.8 ³	—	—	
iso-Amyl	.	104.7-104.9/770	0.8665	1.3981	0.690 ₁	89.83	7	—	—	—	
(c) Propionates—											
Methyl	.	80.1/763	0.9086	1.3750	0.613 ₈	54.66	7	54.66 ³	65.75	66.02 ₅	
Ethyl	.	98.3/766	0.8845	1.3816	0.643 ₈	60.43	10.73	7	—	—	
iso-Amyl	.	161.3/764	0.8632	1.4043	0.705 ₄	—	—	—	—	—	
(d) Butyrates—											
Methyl n-	.	102.5/762	0.8909	1.3851	0.644 ₆	65.83	9	65.99 ⁵	77.43	77.54 ₅	
Ethyl n-	.	120.9/763	0.8736	1.3902	0.660 ₈	77.43	10	—	78.32	77.54 ₅	
Ethyl iso-	.	109.9/764	0.8642	1.3854	0.671 ₈	78.32	11	—	113.52	13	
iso-Amyl n-	.	177.3-177.7/757	0.8591	1.4085	0.717 ₄	—	—	—	—	—	
(e) Valerates—											
n-Amyl	.	—	—	1.4106	0.723 ₈	124.55	12	127.5 ⁹	—	—	
(f) Benzoates—											
Methyl	.	198.4-198.6/760	1.0832	1.5145	0.590 ₈	81.59	9	82.6 ¹⁷	93.32	98.2 ¹⁷	
Ethyl	.	211.4/763	0.9449	1.5036	0.621 ₁	105.01	10	—	116.69	9	
* Propyl	.	229.4-229.6/770	1.0191	1.4967	0.639 ₈	—	—	—	—	—	
n-Butyl	.	247.8-248.0/754	1.0019	1.4953	0.654 ₈	—	—	—	—	—	
4. Hydrocarbons:											
Benzene	.	—	—	1.4980	0.702 ₃	54.85	12	54.6 ¹⁸	54.7 ¹²	—	
Toluene	.	80.2/767	0.8731	1.4910	0.777 ₄	66.10	10	54.8 ¹⁰	54.9 ¹⁰	54.96 ³¹	
		110.6/768	0.8581	—	—	—	—	55.0 ²²	55.6 ²²	55.6 ¹⁸	
		—	—	—	—	—	—	66.4 ²²	65.6 ¹⁸	66.4 ²²	

* Corrected for 0.35% of contained water; exptl. val. 0.529°.

† Kindly presented by Dr. A. E. Bradford.

‡ Measurements made on supercooled liquid, f.p. 24.04°.

§ The probable error in χ_e estimated in the usual way, is less than 1 part in 1000.

¶ Measurements made on supercooled liquid, f.p. 24.04°.

The mean value of χ_M is -0.660 and the error of the mean is

$$\pm 0.07 \sqrt{\frac{1}{n(n-1)}} = \pm 0.0005,$$

leading to a value of -21.15 for the molecular susceptibility (mol. wt. 32.042).

The data so far obtained are collected in Table III.

Some aldehydes and ketones have also been examined by Mr. Emyr Roberts, but the data on these series do not show the same self-consistency as the series in Table III and, accordingly, they are withheld until they can be confirmed. The aldehydes appear to yield a slightly lower and the ketones a slightly higher value for χ_{OM} than that now reported.

Discussion.

Before discussing the derivation of χ_{OM} from the data in Table III there are several noteworthy features to which attention is directed :—

(i) it will be observed there is a definite difference between the molecular susceptibilities of a *normal* compound and its *iso*-isomeride ; *

(ii) *iso*- and *sec*.-isomerides * have approximately the same values of χ_M ;

(iii) conversion of an acid into its methyl ester yields a value of χ_{OM} approximately 1 unit (numerically) less than the value deduced from the various series, i.e., -10.66 instead of -11.69 . This last observation does not appear to have been made by previous workers, who, in fact, report an increase of the normal magnitude in passing from acid to methyl ester. Nevertheless, the excellent agreement between the values of χ_M now recorded and recent data of other workers (e.g., acetic acid : -31.52 ; -31.8 ; -31.9 ; this paper -31.72) and the self-consistency of the data, particularly on esters, afford strong support for believing that the reported anomalous value of χ_{OM} is real. (See also Part III.)

To deduce the value of χ_{OM} from the values of χ_M in Table III it is possible to proceed by two methods, due to Pascal ¹⁸ and to Farquharson and Sastri, ¹⁹ respectively. Both have been used and both yield practically the same result, but the method of Farquharson and Sastri is preferred for reasons which will be given.

¹⁸ Rao and Narayanaswamy, *Proc. Indian Acad. Sci., A*, 1939, 9, 33.

¹⁹ Cabrera and Mandinavoiria, *Ann. Soc. Esp. fis. quim.*, 1932, 30, 528.

²⁰ Henrichsen, *Ann. Physik*, 1898, 34, 180.

²¹ Varadachari, *Proc. Indian Acad. Sci., A*, 1935, 2, 101.

²² Nevgi, *J. Univ. Bombay*, 1938, 7, 74.

²³ Kido, *Sci. Rep. Tohoku Univ.*, 1932, 21, 385; 1933, 22, 835; *Rep. Yokohama Tech. Coll.*, 1934, No. 2, 203.

²⁴ Mathur, *Indian J. Physics*, 1931, 6, 207.

²⁵ Bhatnagar and Mathur, *Phil. Mag.*, 1931, 11, 914.

²⁶ Kido, *Rep. Yokohama Tech. Coll.*, 1934, No. 2, 203.

²⁷ Cabrera and Fahlenbrach, *Z. Physik*, 1934, 89, 682.

²⁸ Pascal, *Compt. rend.*, 1909, 149, 342.

²⁹ Boeker, *Physic. Rev.*, 1933, 43, 756.

³⁰ Rao and Sivaramakrishnan, *Indian J. Physics*, 1931, 6, 509.

³¹ Salceanu and Gheorghiu, *Compt. rend.*, 1935, 200, 120.

³² Rao and Varadachari, *Proc. Indian Acad. Sci., A*, 1934, 1, 77.

³³ Ranganadhan, *Indian J. Physics*, 1931, 6, 421.

³⁴ Pascal, *Compt. rend.*, 1925, 180, 1596.

³⁵ Rao, *Indian J. Physics*, 1934, 8, 483.

³⁶ Kido, *Rep. Yokohama Tech. Coll.*, 1934, No. 2, 233; *Sci. Rep. Tohoku Univ.*, 1936, 24, 701.

* The susceptibility of isomerides is discussed in Part III

In the Pascal method individual values of χ_{OH_2} are obtained by subtracting χ_M of a compound from χ_M of its next higher homologue. The values thus obtained are then averaged for the series so that, virtually, the value is obtained by subtracting χ_M for the lowest homologue from χ_M for the highest and dividing by the number of interposed $>CH_2$ groups; values for intermediate members are neglected. Consequently, the accuracy of χ_{OH_2} will depend entirely on the accuracy of χ_M for the lowest and highest homologues, and, thus, ultimately on the purity of these compounds. Application of this method to the series in Table III yields a mean value (from 31 individual values; extreme values: -11.29 and -11.95) for χ_{OH_2} of -11.68 \pm 0.02.

On the other hand, the method of Farquharson and Sastri involves the using of individual values of χ_M for each member of the series. Values of χ_M are plotted against n , the number of $>CH_2$ groups in the molecule. The straight line obtained can be represented by the equation $\chi_M = n\chi_{OH_2} - b$, where b , the intercept on the χ_M axis, represents the susceptibility of the member of the series with $n = 0$. Plots of χ_M against n for the various series yield appropriate values of b and by subtracting b from any χ_M value the contribution due to $n \cdot \chi_{OH_2}$ is obtained and hence the diamagnetic increment of the $>CH_2$ group. When the method is applied to the present results the values in Table IV are obtained; details are given for alcohols only.

TABLE IV

								Mean $- \chi_{OH_2}$
1. Alcohols. (General formula— $(CH_2)_nOH_2$).								
	Normal.						Branched.	
n	.	1	2	3	4	3	4	5
— χ_M	:	21.15	33.95	44.44	56.15	45.68	57.21	68.96
— b	:	9.5	9.5	9.5	9.5	10.5	10.5	10.5
— $n\chi_{OH_2}$:	11.65	23.55	34.94	46.65	35.18	46.71	58.46
— χ_{OH_2}	:	11.65	11.77	11.65	11.66	11.73	11.68	11.69
2. Acids. (General Formula— $(CH_2)_nHCO_2H$).								11.71
3. Methyl Esters. (General Formula— $(CH_2)_nHCO_2CH_3$).								11.69
4. Acetates. (General Formula— $CH_3CO_2H(CH_2)_n$).								11.69
5. Ethyl Esters. (General Formula— $(CH_2)_nHCO_2C_2H_5$).								11.65
6. Propionates. (General Formula— $C_2H_5CO_2H(CH_2)_n$).								11.67
7. Butyrates. (General Formula— $C_3H_7CO_2H(CH_2)_n$).								11.69
8. Iso-Amyl Esters.								
						CH ₃		
						CH ₃		
9. Benzoates. (General Formula— $C_6H_5CO_2H(CH_2)_n$).								11.71
10. Esters. (Normal.)								11.70
11. Esters. (Iso-)								11.69

In all, 57 individual values of χ_{OH_2} were used (ranging from -11.60 to -11.78) and the mean value is -11.69 \pm 0.003. Not only does this method take into consideration individual values of χ_{OH_2} but it leads

to obtaining almost twice as many χ_{OH_2} values as the Pascal method applied to the same data. The constancy of χ_{OH_2} for the various series and the close agreement between the mean values of χ_{OH_2} from the two methods lead us to believe that the data are self-consistent and accurate.

A further test of the accuracy of the data may be applied by comparing the values of b with recorded values for the compounds represented by b in the various series. The comparison is made in Table V.

TABLE V

Series.	b .	Formula and Name of Compound represented by "b".	Recorded Values (χ_M).
1. Alcohols .	9.5	H. OH	12.06
2. Acids .	20.0	H. CO ₂ H	19.0 ^a ; 19.03 ^b ; 20.0 ^c ; 20.5 ^d ; 20.57 ^e
3. Methyl esters .	30.7	H. CO ₂ C ₂ H ₅	31.4 ^f ; 31.6 ^g ; 32.4 ^{h, i, j} ; 33.62 ^k
4. Acetales .	30.7	CH ₃ CO ₂ H	31.72 (this paper)
5. Ethyl esters .	42.4	H. CO ₂ C ₂ H ₅	42.4 ^l ; 43.0 ^m ; 43.43 ⁿ
6. Propionates .	42.4	C ₃ H ₇ CO ₂ H	43.36 (this paper)
7. Butyrates .	54.1	C ₄ H ₉ CO ₂ H	55.2 (this paper)
8. iso-Amyl esters .	78.1	H. CO ₂ CH ₂ . CH ₂ . CH(C ₂ H ₅) ₂	iso-Amyl formate 78.38 (this paper)
9. Benzoates .	69.9	C ₆ H ₅ CO ₂ H	67.78 ^p ; 70.2 ^q
10. n-Esters .	10.0	HCO ₂ H	Formic acid See Series 2
11. iso-Esters .	20.0	HCO ₂ H	Formic acid See Series 2

For alcohols, the final member is H(OH) and $b = 9.5$. This is considerably different from the value for water but close agreement might not, in this instance, be expected. The agreement between the values of b for acids, and methyl, ethyl, and iso-amyl esters and the recorded values for the compounds represented by b is extremely close. The intercepts for acetates, propionates, and butyrates represent the corresponding acids and it is noteworthy that, for each series, the value of b is approximately one unit less than the experimental value for the acid. This supports the fact, previously referred to, that the diamagnetic increment for conversion of an acid to its methyl ester is — 10.7, one unit less than the average value for homologous series and thus the intercepts for esters will be one less than the corresponding acids. A

^a Rao and Sriraman, *Phil. Mag.*, 1937, 24, 1625.

^b Rao and Sriraman, *J. Annamalai Univ.*, 1938, 7, 187.

^c Pascal, *Ann. Chim.*, 1910, 19, 5.

^d Pascal, *Bull. Soc. Chim.*, 1911, 9, 177.

^e Koenigsberger, *Ann. Physik*, 1898, 66, 698.

^f Gray and Birse, *J. Chem. Soc.*, 1914, 105, 2707.

^g Kido, *Sci. Rep. Tohoku Univ.*, 1936, 24, 701.

similar behaviour should be shown by the benzoates but the agreement between recorded values for benzoic acid is not sufficiently good to test this. *Normal* esters give a value of b , one unit lower than the recorded value for formic acid as would be expected. The *iso*-esters, however, yield the value of -20.0 for formic acid. It is shown in Part III that *iso*-compounds are approximately one unit more diamagnetic than the *n*-isomerides.

The close correspondence exhibited in the various series does lend further support to the view that the data are accurate.

Summary.

The diamagnetic susceptibilities of 39 highly-purified liquids have been measured by the Gouy method under carefully-controlled conditions of measurement. The compounds examined are members of homologous series, and analyses of the data by the Pascal subtraction method and by the graphical method of Farquharson and Sastri yield values of -11.68 ± 0.02 and -11.69 ± 0.003 , respectively, for the diamagnetic increment of the $>\text{CH}_3$ group. The latter method is considered the more accurate. Conversion of an acid into its methyl ester yields a value of -10.66 for χ_{m} . An *iso*-compound is more diamagnetic than its *n*-isomeride.

PART III. THE DIAMAGNETIC SUSCEPTIBILITY OF ISOMERIDES.

That isosteric molecules exhibit similarities in physical properties is well known, and finds confirmation in the reported identity of the magnetic susceptibilities of carbon monoxide and nitrogen.¹ It might, therefore, be expected, particularly from the standpoint of Pascal's additivity rule, that organic isomerides should likewise show identical susceptibilities, and many recorded data confirm this view. For example, Pascal² found identical values for each of the pairs: *n*-butyraldehyde—methyl ethyl ketone; ethyl aniline—dimethylaniline; methyl benzoate—phenyl acetate. More recently Bhatnagar and Dhawan³ and Bhatnagar, Mitra and Tuli⁴ have extended the list.

On the other hand, however, a considerable number of isomeric substances of non-identical susceptibilities have been reported. Frequently

TABLE I

<i>iso</i> -Propyl alcohol	>	<i>n</i> -propyl alcohol	1.50^5 ; 1.21^6 ; 0.90^7
<i>iso</i> -Butyl alcohol	>	<i>n</i> -butyl alcohol	0.96^8 ; 0.74^8 ; 0.80^8
<i>iso</i> -Butyric acid	>	<i>n</i> -butyric acid	$1.59^{5,6}$; 1.67^8
<i>iso</i> -Butyl bromide	>	<i>n</i> -butyl bromide	$2.74^{5,8}$
Methyl <i>iso</i> -butyl ketone	>>	methyl <i>n</i> -butyl ketone	0.70^1
Ethyl <i>iso</i> -butyl ketone	>	ethyl <i>n</i> -butyl ketone	0.80^2
<i>tert</i> -Butyl alcohol	>	<i>iso</i> -butyl alcohol	0.37^4
Methyl <i>tert</i> -butyl ketone	>	methyl <i>iso</i> -butyl ketone	0.60^2
Ethyl <i>tert</i> -butyl ketone	>	ethyl <i>iso</i> -butyl ketone	0.30^2

¹ Caven, *Structure of Matter*, 1924, p. 156.

² Pascal, *Ann. Chimis.*, 1910, 19, 5.

³ Bhatnagar and Dhawan, *Phil. Mag.*, 1928, 5, 536.

⁴ Bhatnagar, Mitra and Tuli, *ibid.*, 1934, 18, 449.

⁵ Bhatnagar and Mathur, *ibid.*, 1931, 11, 914.

⁶ Bhatnagar, Mathur and Mal, *ibid.*, 1930, 10, 101.

⁷ Azim, Bhatnagar and Mathur, *ibid.*, 1933, 16, 580.

⁸ Bhatnagar, Mathur and Nevgi, *Z. Physik*, 1931, 69, 373.

⁹ Mathur, *Indian J. Physics*, 1931, 6, 207.

data on isomerides cannot be compared because they have not been obtained by the same investigator. Table I is, therefore, restricted to those isomerides for which comparison is possible and the extent of the recorded difference is given (- indicates larger diamagnetism).

TABLE II

Compound.	χ_M
$C_3H_6O_2$	42.48
	42.37
	43.30
$C_4H_8O_2$	54.00
	54.06
	55.20
	56.00
$C_5H_{10}O_2$	65.83
	65.91
	65.75
	65.83
	66.79
	67.04
$C_6H_{12}O_2$	77.47
	77.43
	78.55
	78.38
	78.52
	78.32

It will be noted that *iso*-compounds are more diamagnetic than *n*- and less diamagnetic than *tert*- compounds; but it will also be noted that there is quite considerable variation in the magnitude of the differences. Thus, for the propyl and butyl alcohols, Bhatnagar and his students at different times record differences which do not accord very well with each other. From these data it does appear that the differences between *iso*- and *n*-isomerides are greater than those between *tert*- and *iso*-isomerides.

TABLE III

Compound.	$-(\chi_{iso} - \chi_n)$.
Propyl alcohol	45.68 - 44.44 1.24
Butyl alcohol	57.21 - 56.15 1.06
Butyric acid	56.06 - 55.20 0.86
Butyl formate	66.79 - 65.83 0.96
Propyl acetate	67.04 - 65.91 1.13
Butyl acetate	78.52 - 77.47 1.05
Ethyl butyrate	78.32 - 77.43 0.89

Experimental Data.

In Part II data on a number of isomerides have been given. Examination of Table II shows clearly that (acids apart) isomerides for which the extent of chain-branching is the same (bracketed) have identical susceptibilities.

The influence of chain-branching is shown in Table III.

The values given in Table III are much more constant than those previously reported (*vide* Table I), and it would appear that the susceptibility of the *iso*- is approximately one unit greater than that of the *n*-isomeride.

The four butyl alcohols have been examined and the sequence is :

$$\begin{array}{ccccccc} \text{terti.-} & > & \text{sec.-} & > & \text{iso-} & > & \text{n-} \\ - \chi_M = 57.42 & & 57.30 & & 57.21 & & 56.15 \\ - \Delta \chi_M = & & 0.12 & & 0.09 & & 1.06 \end{array}$$

Discussion.

The data summarised tabularly in the preceding section not only extend the observations of Bhatnagar and his collaborators^{4, 5, 6} on *n*- and *iso*-isomerides but raise an entirely new aspect of anomalous dia-

magnetism of isomeric compounds, *viz.*, the differences between isomeric monocarboxylic acids and esters.

The data in Table III show that $\chi_{M^{\circ}}$ for the seven pairs investigated, is greater than χ_n by an almost constant amount. In their discussion on this type of isomerism Bhatnagar *et al.* show that the isomeride with lower boiling-point is the more diamagnetic, and, with this observation, the present data are in complete agreement. They also show that :—

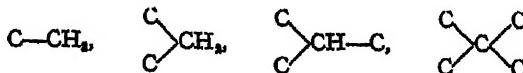
(i) the more diamagnetic isomeride has the higher value of the molecular magnetic rotation (Perkin¹⁰) ; (ii) the diamagnetism is greater in the isomeride having the higher value of the depolarisation factor “ r ” observed by Krishnan¹¹ and Ganesan¹² and (iii) diamagnetism increases with increased molecular volume using Lossen’s values.¹³

It will be noted from Table IV that the more diamagnetic (*iso*-) isomeride has lower values for boiling-point, density, and refractive index.

TABLE IV

Compound.	$-\chi_M^{\circ}$	B.p. (°C/min.).	ρ_4^{25}	n_D^{25}
<i>n</i> -Propyl alcohol	44.44	96.8/748	0.7999	1.3834
<i>iso</i> -Propyl alcohol	45.08	80.8/763	0.7969	1.3756
<i>n</i> -Butyl alcohol	56.15	116.7/748	0.8063	1.3076
<i>iso</i> -Butyl alcohol	57.21	107.2/764	0.7983	1.3932
<i>n</i> -Butyric acid	55.20	162.2/762	0.9351	1.3950
<i>iso</i> -Butyric acid	56.06	153.2/762	0.9442	1.3912
<i>n</i> -Butyl formate	65.83	106.1/754	0.8864	1.3871
<i>iso</i> -Butyl formate	66.79	97.1/745	0.8772	1.3835
<i>n</i> -Propyl acetate	65.91	101.4/760	0.8811	1.3821
<i>iso</i> -Propyl acetate	67.04	87.1/753	0.8629	1.3748
<i>n</i> -Butyl acetate	77.47	125.5/753	0.8749	1.3922
<i>iso</i> -Butyl acetate	78.52	116.8/770	0.8645	1.3877
Ethyl <i>n</i> -butyrate	77.43	120.9/763	0.8736	1.3902
Ethyl <i>iso</i> -butyrate	78.32	109.9/764	0.8642	1.3854

The reality of the existence of such a difference between χ_M° of isomeric pairs would appear to be unquestionable and the tacit assumption generally made that *n*- and *iso*-isomerides yield identical values for an additive physical property is, therefore, wrong. Recently attention has been directed to this question by Gibling¹⁴ in a discussion of parachor values, and he concludes that “interference corrections” must be introduced for chain-branching on account of the electronic disorganisations resulting from the “proximity of atoms or groups in the molecules.” He thus derives “group values” for such groups as



and, using his derived values, obtains calculated parachors in very good agreement with experimental values, and, in the few cases where it is possible to make the comparison, the *iso*-compound has a slightly lower parachor than the *n*-isomeride.

That chain-branching does lead to electronic disorganisation is further

¹⁰ Perkin, *J. Chem. Soc.*, 1884, 45, 575, *et seq.*

¹¹ Krishnan, *Phil. Mag.*, 1925, 50, 697.

¹² Ganesan, *ibid.*, 1925, 50, 1219.

¹³ Lossen, *Annalen*, 1889, 254, 42.

¹⁴ Gibling, *J. Chem. Soc.*, 1941, 299.

evidenced by observations on Raman effect. Kohlrausch and Köppel¹³ found that Raman displacements attributable to the hydrocarbon chain have slightly lower values in *iso*-compounds. Collins¹⁴ noted in his investigation on the Raman spectra of octanols that the form and location of the displacement 1300 cm.⁻¹ were altered slightly by branched methyl substitution.

When the differences between isomeric acids and esters are considered it is found that the acid is invariably approximately one unit more diamagnetic than the ester. It is also found that relationships between χ_M and boiling-point, density, and refractive index are quite different from those to which attention has been drawn (Table IV) for the *n*- and *iso*-isomerides. It must, therefore, be concluded that these relationships are either valid only for *n*- and *iso*-isomerism or are entirely fortuitous. A decision cannot at present be reached; it is felt, however, that too much emphasis should not be placed on these relationships between various physical properties until more carefully-determined data are available.

It has already been shown in Part II that the diamagnetic increment for the $>\text{CH}_3$ group is identical for the acid and ester series and, thus, the contributions of the hydrocarbon chains are the same. Moreover, for esters, it was shown that the value of χ_{on} was the same irrespective of whether the series is ascended through R or R' in $\text{RCO}_n\text{R}'$. Clearly then the anomalies are due to a difference in the structure of the "carboxyl" group in the acids and esters. This is in keeping with recorded observations on other structural properties. For example, Zahn¹⁵ draws similar conclusions from investigations on the electric moments of carboxylic acids and their esters. Also, it is well known that the Raman frequency associated with the C=O group has quite different values in carboxylic acids and esters.

In a recent article Gibling,¹⁶ using his "standard values" method¹⁴ for determining parachors, derives the value 259.8 for the parachor of the dimeric form of acetic acid. Assuming that the value for the monomeric form will be half of this, 129.9, we can compare this with the value of methyl formate, for which he gives 138.0. Similarly it is found that *n*-propionic and -butyric acids have smaller parachors than ethyl and *n*-propyl formates. This is particularly interesting because, just as was the case with the *normal-iso*-isomerism, the isomeride with the greater diamagnetism has the lower parachor. Thus it would appear that there is some connection between diamagnetism and molecular volume and that diminution in molecular volume causes an increased diamagnetism, although Bhatnagar--probably owing to using the older data of Lossen--draws the opposite conclusion.

At the present juncture, with so few data, any attempt to explain the anomalies quantitatively would be unjustified even if a precise treatment were possible. Obviously such a treatment will present very great difficulty even after many more confirmatory data have been obtained. One justifiable conclusion can, however, be drawn. Diamagnetic susceptibilities are additive, but constitutive effects play a more dominant rôle than has hitherto been suspected.

It is confidently expected that the contemplated extensions of these investigations will confirm the view that the greatest usefulness of diamagnetism in problems of molecular structure will accrue by assigning values to groups of atoms, rather than to individual atoms, in a manner analogous to, if not identical with, that adopted by Gibling¹⁴ in regard to parachor.

¹³ Kohlrausch and Köppel, *Z. physikal. Chem. B*, 1934, 26, 209.

¹⁴ Collins, *Physic. Rev.*, 1932, 40, 829.

¹⁵ Zahn, *Trans. Faraday Soc.*, 1934, 30, 804; *Physic. Rev.*, 1931, 37, 1516; *Physikal. Z.*, 1932, 33, 730.

¹⁶ Gibling, *J. Chem. Soc.*, 1942, 665.

Summary.

The diamagnetic susceptibility of an isomeride with a branched hydrocarbon chain is greater than that of the corresponding straight chain compound, and the sequence appears to be *tert.*- slightly *sec.*- $>$ *iso-* $>$ *n.* For *n*- and *iso*-isomerides the more diamagnetic compound has the lower values for boiling-point, density, and refractive index. The *iso*-compound is approximately one unit more diamagnetic than the *n*-isomeride. Monocarboxylic acids are more diamagnetic (by approximately one unit) than isomeric esters. Evidence is adduced to show that the more diamagnetic isomeride has the smaller molecular volume.

It is a pleasure to express our thanks to Professor J. L. Simonsen, F.R.S., for his interest in the work.

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THE PHYSICO-CHEMICAL BASIS OF MITOGENETIC RADIATION.

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In the last two or three years the weakest part in the study of mitogenetic radiation—the explanation of its energetic basis—has acquired a firm foundation. This is due, on the one hand, to the far-reaching investigations of R. Odyuber, carried out by a purely physical method (photon counter). These investigations confirmed some of our old data on radiation in chemical reactions and in several biological objects (the eggs of amphibia during division and excited nerves); and on being communicated by him to the Faraday Society conference in 1939, met with recognition and evidently removed the last doubts as to the possibility of discovering mitogenetic radiation by purely physical methods.

On the other hand, investigations and calculations carried out by us, respecting the balance of energy in several reactions serving as a common source of mitogenetic radiation, have shown that extremely simple and plausible considerations are excellently confirmed by experiment; this removes the apparent difficulties which arose from a purely physical standpoint in discussing the possible origin of such short-wave ultraviolet light in weak exothermal or even thermally neutral reactions to which belong fermentative processes—the usual sources of the radiation.

At the basis of our investigations lay considerations advanced in 1934 by the photochemist, Frankenburger.

The energy (heat content) of chemical processes necessary for the appearance of the photons up to 150 kg. cal. = 1900 Å., discovered by mitogenetic spectrum analysis, can come only from the recombination of free radicals or atoms. In such an elementary act one of two things can take place: either the energy is given off directly in the form of a photon, or it is absorbed by the molecules in the system and then released in the form of radiation (fluorescent radiation) with wavelengths (spectrum) characteristic of the given substance. Taking into consideration the diversity of the spectra observed by us, he was more favourably inclined towards the second possibility.

As to the presence of free radicals, he took the viewpoint of Willstätter's and Gaber's hypothesis, which assumes that in a number of fermentative processes free radicals appear as an accessory or accompanying phenomenon in minute quantities, quite sufficient, however, if one takes into consideration the insignificantly small intensity of mitogenetic radiation.

The main assumption of this hypothesis has been directly confirmed by a number of experiments published by us in concise form. If the energy released in a recombination process is really absorbed and then emitted as fluorescence by various kinds of molecules in the given solution then the following experiment should be feasible. Some substance known not to take part in the given reaction is added in insignificant concentrations to the system : ferment and adequate substrata. However, in the mitogenetic spectrum accompanying the fermentative reaction, new bands should appear characteristic of the emission spectrum of the added substance. Numerous experiments carried out with various fermentative systems, with the addition of different organic substances (*e.g.* glucose and indoline) and ions (sodium chlorido, sodium biphosphate and others), have fully corroborated expectations.

On the basis of those data we are forced to change our original explanation of mitogenetic spectra : up to now we regarded them as a direct correlate or proof of the presence of a given chemical process (*e.g.* glucolysis, proteolysis, etc.). As a matter of fact, however, we are dealing with the fluorescence spectra of some substance or other whose molecules have been excited by absorbing the recombination energy of radicals (atoms), which themselves seem to remain in the background.

It is much more difficult to check experimentally Frankenburger's second principal thesis—the appearance of radicals in fermentative reactions. As N. N. Semyenov has correctly observed, the main assumption is incorrect on thermodynamic considerations ; *i.e.* in essentially thermo-neutral reactions such as fermentative processes, the concentrations of radicals in the reacting systems cannot be greater than in the corresponding solutions not containing ferments if the viewpoint that these latter are merely catalysts is correct.

If the radiation in fermentative processes does arise due to the recombination of radicals, then it is necessary to consider additional energy exchange processes to which no attention has yet been paid.

Indeed, the investigations of three fermentative systems undertaken from this point of view—the splitting up of peptides under the influence of peptidase, of urea by urease, and of glucose by zymase—have shown that mitogenetic radiation arises in these processes only in the presence of atmospheric oxygen in all three cases and, in addition, of visual light in the first two systems, two photons of visual light participating in each elementary act, *i.e.* in the splitting up of one substrata molecule. This conclusion is reached from the following experimental data :

A series of earlier investigations had already established that the minimum time of irradiation of the biological detector necessary for evoking the mitogenetic effect was proportional to the intensity of the source of radiation.

In our present experiments we succeeded in showing that when the detector is irradiated by fermentative systems—the splitting up of peptide or urea—the corresponding time limits are inversely proportional to the square of the intensity of the visual light used in the experiments. Thus, for instance, for a total intensity of the lamp used the time limit of exposure was equal to one minute (allowing an error up to 15 %) while a reduction to one-half the intensity brought the time limit up to four minutes, with the same degree of accuracy. This dependence on the square of the intensity can only be explained in the following manner : if the probability that a reacting molecule absorbs one photon is equal to $1/p$, then the probability that two photons will be absorbed will equal $1/2p$.

This statement is also corroborated in an entirely different way by calculating the energy balance of the reaction, taking into account the formation of new radicals whose recombination serves as the source of the radiation energy.

Here we have recourse to a calculation based on a permissible fiction. Suppose that in a fermentative reaction the substrata completely breaks up into atoms and simple radicals. The total expenditure of energy can be easily calculated from data on the heat content of the individual binding⁴. To this expenditure we add the energy spent on splitting up the water molecule and molecular oxygen which figure in the balance of energy when the system is irradiated during the reaction.

We shall carry out a similar calculation of the energy balance in case when such products of fermentative decomposition are formed from the resulting radicals (atoms) which can be registered by the usual chemical methods. Fermentative reactions are usually slightly exothermic, i.e. assuming complete disintegration of the molecule the positive balance exceeds our calculated energy expenditure by several kg. cal.

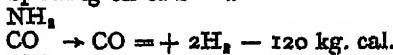
Together with this calculation we make the following basic assumption: in addition to the products of fermentative disintegration registered by the usual methods, there also arise in very small concentrations (i.e. as rare events, unsusceptible to chemical analysis) substances also rebuilt out of atomic radicals.¹ In these processes there remain unused several categories of atoms and radicals, whose recombination is the source of the mitogenetic radiation energy.²

However, the energy balance in these assumed processes of synthesis is insufficient, i.e. the energy released does not cover the calculated total amount spent on splitting up the substrata. This circumstance explains why in certain reactions a realisation of the assumed processes demands, besides oxygen, photons of visual light, the difference between the positive and negative energy balances allowing the limit of active light to be calculated on the long-wave side.

We give the details of such a calculation for a simpler fermentative process—the disintegration of urea by urease.

I. Energy expenditure—

(1) Splitting off of 2 — x



NH_3

(2) $\text{H}_2\text{O} \rightarrow \text{H} + \text{H} + \text{O} - 220 \text{ kg. cal.}$

(3) $\text{O}_2 \rightarrow \text{O} + \text{O} - 118 \text{ kg. cal.}$

Total : — 458 kg. cal.

II. Energy-freed in the assumed rare processes—

(1) $\text{NH}_3 + \text{NH}_3 \rightarrow \text{N}_2\text{H}_4$ (hydrazine) + 69 kg. cal.

(2) $2\text{H} + \text{O} \rightarrow 2\text{OH} + 220 \text{ kg. cal.}$

(3) $\text{OH} + \text{OH} \rightarrow \text{H}_2\text{O}_2 + 51.9 \text{ kg. cal.}$

Total : + 491 kg. cal.

The radiation emitted in the process arises at the expense of the CO and O radicals, which remain unused.

However, processes (II) are possible only on condition that there is an additional inflow of energy equal to 17 kg. cal. (458-341 kg. cal.). If we consider this energy to be divided equally between two photons, i.e. each one taking 59 kg. cal., then we can expect that the extreme active wave-length necessary for exciting mitogenetic radiation in the given fermentative reaction will be about 4800 Å. (blue-green light).

Experiment completely corroborates this conclusion. We have already pointed out that the participation of two photons follows from the fact that the mitogenetic effect depends on the square of irradiation by visual light. The calculated long-wave limit of active wave-lengths is confirmed by the data of Table I.

TABLE I. RADIATION OF THE SYSTEM: URINE UREASE UNDER ILLUMINATION BY MONOCHROMATIC LIGHT

Wave-length of applied illumination	.4300 violet	.4800 blue-green	.5000 green
Mitogenetic effects	70%	34%	4%

Entirely analogous reasoning and calculations with respect to the system dipeptide (glycyl-glycine) + crepsine brings to a deficit of 113 kg. cal. corresponding to two 5000 Å. photons (green light). In the given case, a wave-length of 5000 Å. should prove active. Experiment confirms this conclusion too—

Illumination by long wavelengths	5000 Å.	6000 Å.
Mitogenetic effects	63%	6%

Calculations for the third fermentative system glucose-zymase show that the inflow-outflow balances tally if we make several probable assumptions concerning the by-products of recombination, the CO and O radicals remaining unused; the recombination energy of these radicals, equal to 167 kg. cal. is more than sufficient to excite the shortest fluorescence band of the excited glucose molecule, which equals 1000 Å., i.e. 150 kg. cal.

We have shown, in complete agreement with these calculations, that glucolysis is also accompanied by ordinary radiation when the whole system is in the dark. We have succeeded by mitogenetic analysis in establishing the appearance in fermentative reactions and identifying the following radicals: CO, OH and NH₂ (or NH).

Thus, we see that by proceeding from simple and probable assumptions which find diverse experimental confirmation, we are in a position to set up a quite satisfactory energy balance for the emission in organic (fermentative) reactions of medium wave-length ultraviolet light of insignificant intensity, thus depriving the phenomenon of mitogenetic radiation of its puzzling character.

The reverse side of the main mitogenetic problem—the possibility of discovering such insignificant intensities by means of biological detectors—loses all its mystery, if one takes into consideration that the number of ultraviolet photons exciting a mitogenetic reaction in the cell detectors, i.e. in the mitosomes, is of the same order as the limiting number of visual light photons, necessary for exciting visual sensations.

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THE SOLUBILITY OF AMMONIUM BROMIDE IN ALCOHOLIC SOLVENTS.

By M. E. BEDWELL.

Received 31st March, 1943.

The solubility of ammonium bromide in methyl, ethyl and *n*-propyl alcohols at various temperatures has been accurately determined. The available solubility data are scanty. Larson and Hunt¹ have performed similar measurements on the chlorides, bromides, and iodides of sodium and potassium, and Hildebrand² gives data for the alkali metal chlorides and iodides at 25° C.

The theoretical equation of Bjerrum³ has been tested in the case of ammonium bromide at 25° C.

Experimental.

The procedure was similar to that described by Larson and Hunt.¹ The weight of the solute in the saturated solution was determined volumetrically by titration against standard silver nitrate solution.

The solubility measurements were repeated at intervals of 10° between 0° C. and a few degrees below the boiling-point of the solution.

The resulting solubility/temperature curves are shown in Table I and Fig. I. Each curve shows a definite break, which occurs between 30° C. and 40° C.

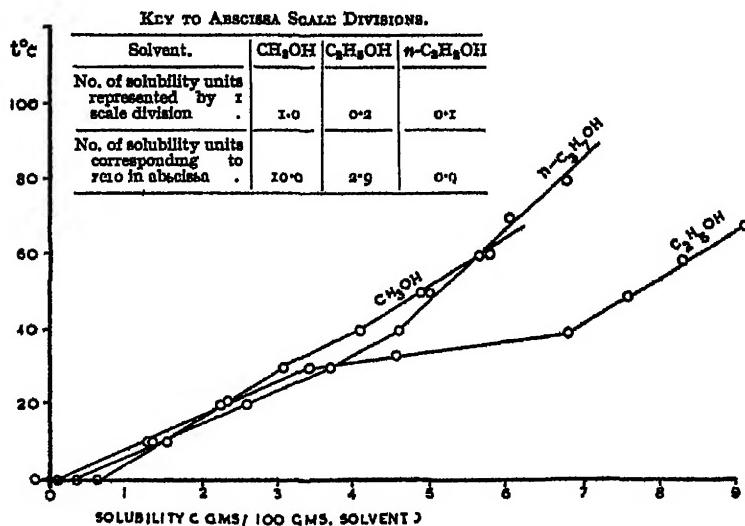


FIG. I.

¹ Larson and Hunt, *J. Physic. Chem.*, 1939, 43, 417-23.

² Hildebrand, *Solubility*, Reinhold, 1936.

³ Bjerrum and Larson, *Z. physik. Chem.*, 1927, 127, 358. Bjerrum and Jozefowicz, *ibid.*, 1932, 159, 194.

TABLE I

Solvent.	Solubility of Ammonium Bromide (g. salt/100 g. Solvent).									
	0° C.	10° C.	20° C.	30° C.	40° C.	50° C.	60° C.	70° C.	80° C.	90° C.
Methyl alcohol .	10.62	11.53	12.33	13.09	14.07	14.88	15.63	-	-	-
Ethyl alcohol .	2.908	3.154	3.350	3.583	3.800	4.112	4.552	4.700	-	-
n-Propyl alcohol	0.9082	1.043	1.158	1.269	1.357	1.397	1.476	1.501	1.570	1.613

Discussion of Results.

The observed change in solubility-temperature coefficient probably indicates a change in the degree of solvation of the salt between 30° C. and 40° C. Bjerrum's theoretical equation⁸ for the solubility of electrolytes was tested, using his method of comparing the mean ionic radius of the dissolved salt (r_m), calculated by the theoretical formula, with the experimental crystal value ($a/2$).

The quantity $(r_m/a/2)$ was found to be a constant (1.21) for saturated solutions of ammonium bromide in methyl, ethyl and *n*-propyl alcohols at 20° C. This constant factor may be attributed to the impossibility of correcting adequately for ionic interaction energy in solutions which are saturated, and therefore relatively concentrated, so that the magnitude of the ionic radius is in error.

A similar constancy was found by Bjerrum and Jozefowicz⁹ who give a mean value of 1.28 ± 0.05 for solutions of tetramethylammonium iodide in water and methyl and ethyl alcohols at 20° C.

Summary.

The solubility of ammonium bromide in the solvents methyl, ethyl, and *n*-propyl alcohols has been accurately determined at intervals of 10° between 0° C. and a few degrees below the boiling-point of the saturated solution.

The solubility/temperature curve for each solvent shows a definite break between 30° C. and 40° C., which is attributed to a change in the degree of solvating power of the solvent.

The Bjerrum equation for the solubility of electrolytes has been tested for solutions of ammonium bromide in the present series of solvents. The results indicate that a constant correcting factor is involved.

The experimental work was performed at Bedford College for Women, University of London (evacuated to Cambridge).

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ELECTRICAL CONDUCTION OF TEXTILES.

By S. BAXTER.

Received 28th April, 1943.

It is well known that textile fibres are hygroscopic and that their electrical conductivity varies according to the amount of moisture absorbed in the fibres. Most of the earlier work on the conductivity of textiles has been concerned with the variation of conductivity with regain at constant temperature; the present work deals with the temperature coefficient of resistance at constant regain and the mechanism of the electrical conductivity.

In the present paper the electrical properties of protein substances and glass fibres with adsorbed vapours are compared and found to very similar. A new theoretical explanation of the results is given on the assumption that dry wool is a perfect insulator, and that adsorbed water molecules can be taken as impurity centres causing the wool to become an electronic semi-conductor.

The theory that the conduction of textile fibres is due to the conductivity of water condensed in the inter-micellar channels breaks down, since the activation energy of a moist wool fibre is totally different from the activation energy for water, showing that the mechanism of the conductivity is different in the two cases. Water present in a textile fibre must, in fact, be in a very different state from liquid water.

Earlier Work.

Marsh and Earp¹ investigated the effect of regain on the conductivity of wool fibres. Using a Lindemann electrometer for the electrical measurements, they found that on plotting log resistance against log regain a straight line was obtained with the equation

$$R = Am^{-15.0},$$

where R is the resistance, m is the regain, and A is a constant. Murphy and Walker,² using wool threads, obtained a relationship similar to that found by Marsh and Earp in which the exponent was -16.4 . Marsh and Earp found that the conductivity of the fibres was independent of whether the fibres were washed in tap water, distilled water, or special conductivity water. The presence of $\frac{1}{2}\%$ olive oil on the fibres had no effect, but the resistance could be decreased by soaking for at least three days in salt solution. These facts show clearly that the conductivity of the wool water system is independent of the conductivity of the water adsorbed by the wool, and suggest that the conductivity is, to a large extent, independent of any ions present in the wool, and arises from the nature of the bonding of the wool and water molecules. Marsh and Earp give experimental values for the variation of the specific resistance of wool with the amount of water adsorbed. The results show that the specific resistance decreases rapidly with increasing regain, and that for 22% regain, i.e. only about 18% of the fibre as a whole is water, the specific resistance has decreased to a value similar to that of conductivity water. For higher regains the specific resistance will tend to a value less than the specific resistance of water. Similar results have been obtained by Stamm³ in experiments on

¹ Marsh and Earp, *Trans. Faraday Soc.*, 1933, 29, 173.

² Murphy and Walker, *J. Physic. Chem.*, 1928, 32, 1761.

³ Stamm, *Colloid Symposia Monograph*, 1926, 4, 246.

wood. The water he used had a conductivity of 5.4×10^{-6} mho., but wood which had adsorbed the same water had a conductivity of 8.3×10^{-6} mho. He concluded that the adsorbed water had about two to three times the conductivity of the water in bulk. These experimental results are contrary to the pore hypothesis of water adsorption which predicts that the specific resistance of textile fibres at all regains should be greater than the specific resistance of the water adsorbed.

The effect of temperature on resistance of textiles has received little attention. Murphy and Walker⁴ investigated the change of resistance with temperature of cotton threads at constant relative humidity. They found that at 25° C. and 76% R.H. the resistance of cotton samples decreases by about 8% per degree C.

Slater,⁵ using single cotton fibres, also found the effect of temperature on resistance at constant R.H., but could not get consistent results. The results he published show that at 25° C. and 57% R.H. the resistance changes by 10% per degree C. change in temperature.

Marsh and Earp found that wool fibres obey Ohm's Law and show no polarisation over the voltage range 0-300 for R.H.'s between 50 and 85%. This has been verified in the present investigations, although earlier workers^{6, 7} using yarns have found that the resistance decreased as the voltage increased. This is, however, probably due to complications introduced by the yarn structure.

Experimental.

The present investigations were mainly concerned with determining the effect of temperature on the conductivity of wool at a constant regain.

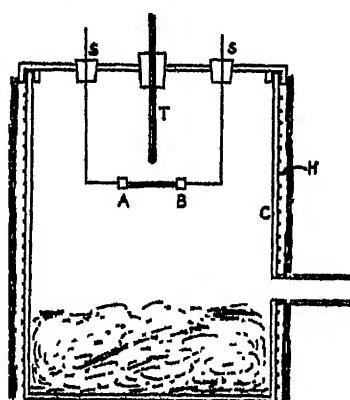


FIG. 1.

filled with air dried over P_2O_5 . Dry air was admitted to ensure that thermal equilibrium within the cylinder was established.

The temperature was controlled by having a heating coil, H, wound round the cylinder, C, which was lagged. The temperature of the enclosure was measured by means of the thermometer, T. The electrical conductivity determinations were made with a Lindemann electrometer, the full circuit being shown in Fig. 2.

The sensitivity of the Lindemann electrometer was varied by altering the plate voltage v_p , the needle when earthed being adjusted to zero by means of the coarse adjusting resistance R_1 , and the fine adjusting resistance R_2 . The voltages were applied to the plates of the electrometer

⁴ Slater, *Proc. Roy. Soc. B*, 1924, 96, 181.

⁵ Curtis, *Bur. Stand. Bull.*, 1914, II, 359.

through the resistances R_5 and R_6 . The electrometer circuit is similar to the circuit developed by Grimmett.⁶

The conductivity of the fibres under measurement was determined in arbitrary units from observations of the rate of charge of the electrometer needle, the needle being de-earthed and connected through the fibres to a voltage v_i . All the essential parts of the circuit were housed in an earthed

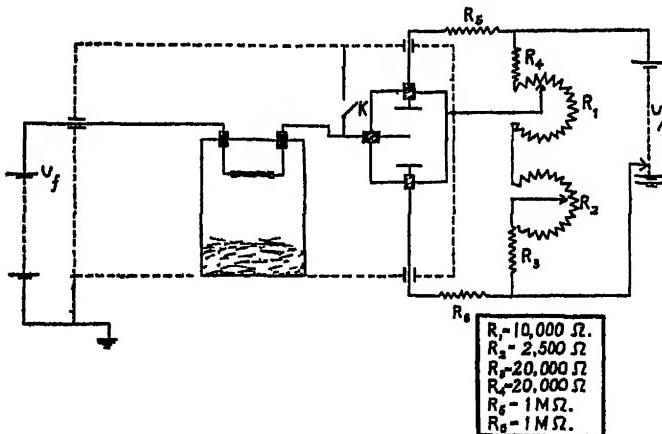


FIG. 2.

cage to prevent trouble from stray electrostatic charges. In the early stages of the work trouble was experienced with insulation, but later sulphur or sealing wax insulation plugs were found to be quite satisfactory.

The wool used in all the experiments was 64s merino which was cleaned by extracting with petroleum ether and then with alcohol followed by washing in distilled water.

Results.

(a) Polarisation Currents at Zero Regain.—It was found that for regains below approximately 5% the wool fibres show polarisation which increases as the regain is decreased. For dry fibres the steady current is approximately 1/5 the initial current for a constant voltage, the time required for a constant current to be established depending on the temperature. Fig. 3 shows the polarisation curves of wool at zero regain at temperatures of 31.5° C., 42.2° C., 53.7° C. and 60.0° C. The time t in secs., which is the time required for the electrometer to charge up to a given value when the needle is de-earthed, is plotted against τ , the time in mins. after application of the voltage v_i . The value of the conductivity is given by $1/t$ in arbitrary units. The steady current was found by obtaining the equation to the t v τ curve, and extrapolating it to find the value of t when τ is infinite. It was found that the polarisation curves fitted the equation

$$t = B - \frac{k_1}{\tau + k_2} \quad \dots \quad \dots \quad \dots \quad \dots \quad (1)$$

where B , k_1 , k_2 are constants. Clearly for $\tau = \infty$, $t = B$, and when the constants of the equation are found the value of t for $\tau = \infty$ can be determined. Using the values of the steady conductivity, i.e. $1/B$, it was found that at zero regain the conductivity increased exponentially with temperature according to the relation

$$\sigma = Ae^{-\frac{B}{kT}} \quad \dots \quad \dots \quad \dots \quad \dots \quad (2)$$

⁶ Grimmett, Proc. Physic. Soc., 1933, 45, 117.

where σ is the conductivity and A and E are constants. If, therefore, $\log \sigma$ is plotted against $1/T$ a straight line is obtained from which can be deduced the value of the activation energy E . Fig. 4 shows $\log \sigma$ plotted

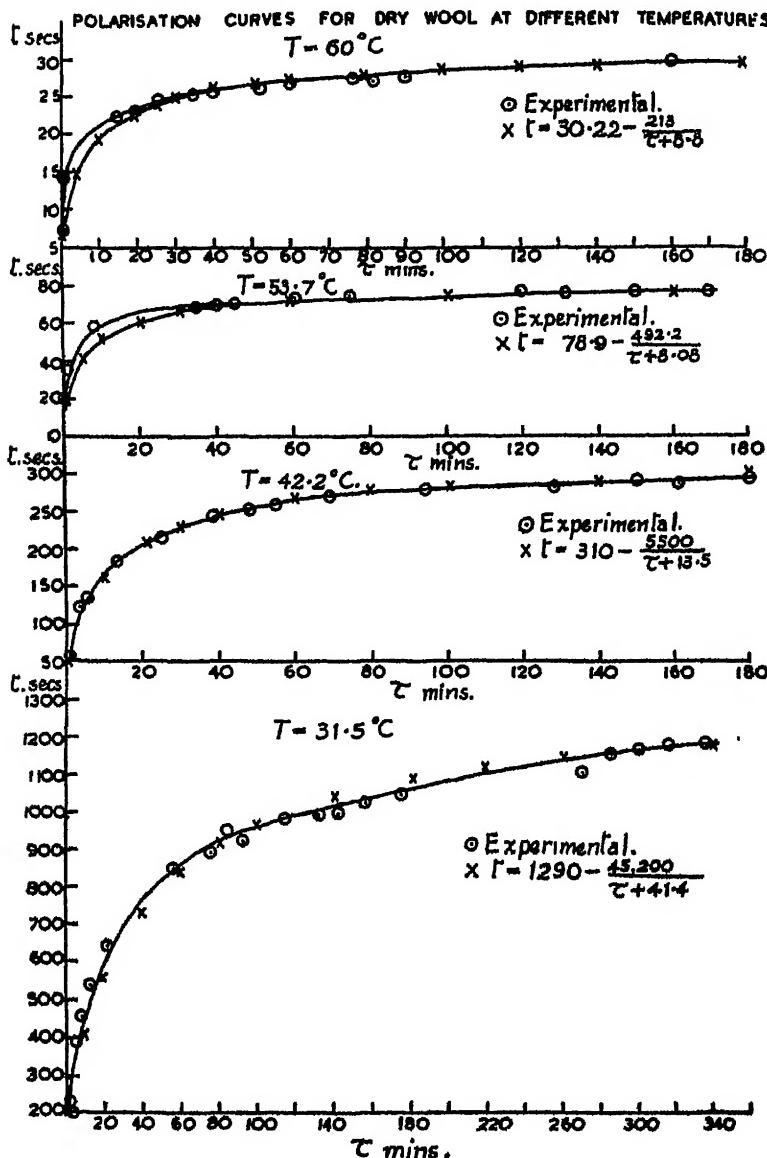


FIG. 3.

against $1/T$, using values of the steady conductivities obtained from the four polarisation curves shown in Fig. 3 for wool at zero regain. The linear relationship is followed, and the slope of the line corresponds to an activation energy of 1.1 e.v.

(b) Activation Energies of Wool, Collagen and Cotton.—As the regain increases from zero the conductivity increases rapidly and the amount of polarisation decreases. This is due to the additional conductivity of the adsorbed water being non-polarisable. As the regain increases the polarisable current of the dry wool becomes swamped by the non-polarisable current due to the adsorbed water, and when the regain is greater than roughly 5 %, the polarisation cannot be detected.

For wool fibres with regains greater than 5 % Ohm's Law is obeyed; this was also found by Marsh and Earp. For a constant regain the temperature coefficient of the conductivity was found to follow equation (2) and by plotting $\log \sigma$ against $1/T$ the activation energy could be obtained. The activation energy for wool for regains greater than 5 % was found to

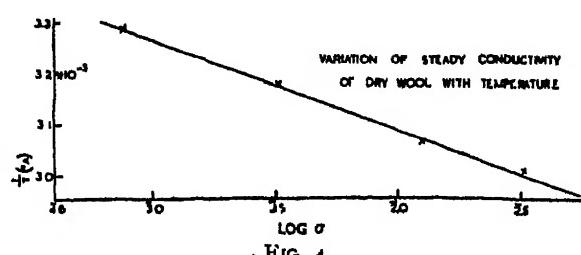


FIG. 4.

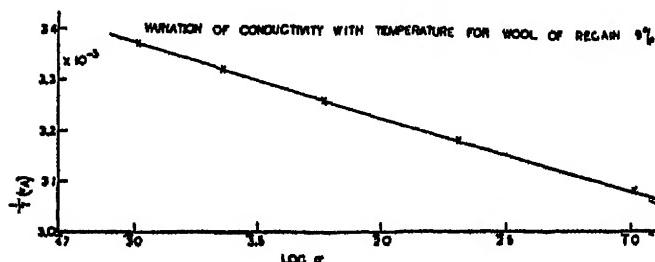


FIG. 5

be independent of the regain, as is shown in Table I. A typical curve of $\log \sigma$ plotted against $1/T$ is shown in Fig. 5, the regain of the wool used being 9 %.

TABLE I.

Regain %.	Activation Energy.
0	1.10 e.v.
3.0	1.39 e.v.
9.0	1.33 e.v.
16.0	1.33 e.v.
28.5	1.35 e.v.

TABLE II.

Activation Energy.	Regain.
Collagen	19.6 %
Wool	9.28 %
Silk	7.5 %
Cotton	6.4 %

The effect of the pH of the wool on the activation energy was investigated, and it was found that the activation energy remained constant from pH 2 to 8,* and then gradually rose to a value of 1.5 e.v. for pH 11.

The activation energies for silk, collagen and cotton were determined, and it was found that all the protein substances gave the same activation energy as is shown in Table II.

* pH of extract when 1 g. of wool is wetted out in 50 c.c. of water.

The temperature coefficient of the conductivity of water corresponds to an activation energy of 0.44 e.v., and for ice to a value of 1.27 e.v.⁷ It is therefore seen that although the conductivity of wool, silk and collagen is due to the presence of adsorbed water the values of the activation energies are very different from the value for liquid water, but are much nearer to the value obtained for ice. Thus it appears that the conductivity in the wool-water system must be of a different nature from the conductivity in pure liquid water. The fact that the activation energy for ice is of the same order as for the wool-water system suggests that the absorbed water is in a much more strongly orientated form than in liquid water. The conductivity in the wool-water system is by no means identical with the conductivity in ice, since ice shows polarisation.

(c) The Wool-methyl Alcohol System.—The effect of the absorption of methyl alcohol on wool was next investigated. The apparatus was evacuated for several hours and the methyl alcohol introduced. The adsorbed methyl alcohol affected the conductivity in much the same way as absorbed water. For any appreciable regain of methyl alcohol the wool-methyl alcohol system obeyed Ohm's Law and showed no polarisation. The variation of resistance with methyl alcohol regain follows the equation

$$R = A m^{-10/3}$$

where A is a constant. The absolute conductivity with absorbed methyl alcohol is of the same order as with an equivalent regain of absorbed water. The activation energy is 1.0 e.v.

The similarity in the effects of absorbed methyl alcohol and water on the conductivity of wool makes it difficult to concede that the conductivity is ionic, and suggests that the wool-water and wool-methyl alcohol systems are electronic semi-conductors. The conduction appears to be due to the water or methyl alcohol appropriately adsorbed by the wool.

(d) Adsorbed Layers on Glass.—In order to test the view that the conductivity may be due to an adsorbed layer, investigations were made on the electrical properties of adsorbed layers on glass surfaces. An adsorbed layer of water on a glass surface was found to have properties very similar to the wool-water system. The resistance varies with the R.H. of the atmosphere due to variations in the thickness of the adsorbed layer. At low R.H.'s polarisation is shown and as the R.H. increases the conductivity increases and the polarisation is swamped. The changes of resistance with R.H. was not as great as in the wool-water system. For the wool-water system an increase of 25 % in the R.H. caused an increase in conductivity of 100 times, whilst for the glass-water system an increase in R.H. of 55 % was necessary to give this increase in conductivity. For a constant amount of adsorbed water the temperature coefficient of conductivity corresponds to an activation energy of 1 e.v. Glass fibres adsorb methyl alcohol with a corresponding increase in conductivity, but experimental difficulties have prevented accurate measurements of the electrical properties of the glass-methyl alcohol systems.

Discussion.

It is difficult to decide whether the electric conductivity of non-metallic solids is ionic or electronic unless a Hall effect can be measured. Other criteria that must be satisfied by electronic conduction are that Ohm's Law should be obeyed and that there should be no polarisation effects. Wool free from water shows large polarisation effects, but the wool-water system has a very much greater conductivity which swamps entirely the polarisation effects shown by dry wool. The wool-water system also follows Ohm's Law. It may, therefore, be an ionic or electronic semi-conductor. There are, however, a number of experimental data that are difficult to

⁷ Dorsey, *Properties of Ordinary Water Substances*, pp. 374 and 509. Reinhold Publishing Corporation, 1940.

reconcile with the hypothesis that the wool-water system is an ionic conductor. There is firstly, the observation of Marsh and Earp that the conductivity of water in wool is greater than that of liquid water. The second observation that is difficult to reconcile with ionic conduction is the large activation energy associated with the wool-water system; it is roughly three times the activation energy that would be expected from the ionic properties of water. Again the activation energy associated with the electric conductivity is independent of the ionic condition of the wool throughout the pH range of 2 to 8; if the conduction were ionic, one would expect the activation energy to be sensitive to pH . Finally, the wool-methyl alcohol system shows an electric conductivity that is similar to the wool-water system. These observations are difficult to reconcile with ionic conduction, whilst they do not conflict with the hypothesis that the wool-water system is an electronic semi-conductor.

Assuming the electrical conductivity in the wool-water system to be due to electronic jumps between bound water molecules, one would expect the resistance to vary exponentially with the average distance between bound water molecules, since on the simple quantum mechanics picture the probability of an electron jump across a potential barrier depends exponentially on the height and width of the barrier. Thus if λ is the mean distance between adjacent water molecules, then for constant temperature

$$R = Ae^{\frac{k}{\lambda}}$$

where A and k are constants. For uniform distribution of the water molecules throughout the wool fibres λ is proportional to $1/\sqrt{m}$ where m is the regain. On this simple hypothesis one would expect the resistance to vary with regain according to the equation

$$R = Ae^{\frac{k}{\sqrt{m}}} \quad \quad (3)$$

where A and k are constants. Marsh and Earp's results of the variation of resistance with regain are found to fit equation (3) quite satisfactorily. Fig. 6 shows Marsh's original values with log resistance plotted against $1/\sqrt{m}$. The linear relationship is seen to hold quite as well as in Marsh's original plotting where log resistance was plotted against log regain. The equation for increasing regain is found to be

$$R = 10^{-3.88} e^{\frac{115}{\sqrt{m}}}$$

and for decreasing regain

$$R = 10^{-7.88} e^{\frac{126}{\sqrt{m}}}$$

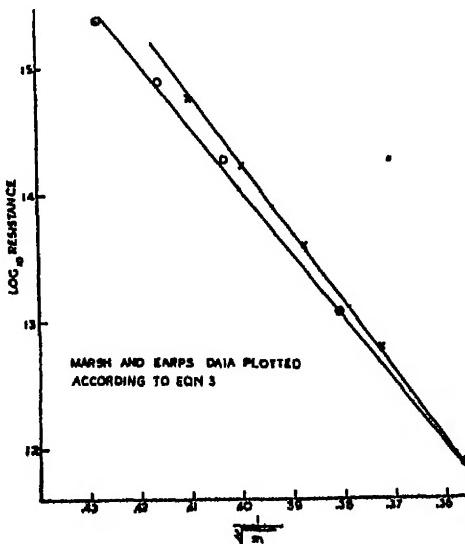


FIG. 6.

Summary.

Experimental results on the electrical properties of textile fibres with and without adsorbed water are given. The temperature coefficient of the electrical conductivity of wool at constant regain has been determined over a wide range of regains and has been found to be independent of regain for values greater than 5 %. For wool fibres below 5 % regain, polarisation is shown, but this disappears for higher regains and Ohm's Law is obeyed. The conductivity of wool with adsorbed methyl alcohol, and for glass fibres with adsorbed water vapour, is found to be similar to the wool-water system.

The theory that the conduction of textile fibres is due to the conductivity of water condensed in the inter-micellar channels does not readily fit the experimental data and a new theory is put forward on the assumption that dry wool is an almost perfect insulator, and that adsorbed water molecules cause impurity centres giving rise to electronic conduction.

I am indebted to Mr. B. H. Wilsdon, Director of Research, for encouragement, and to Dr. A. B. D. Cassie for discussion and suggestions during the course of the work. My thanks are due to the Council of the Wool Industries Research Association for permission to publish the results.

THE MELTING-POINTS AND UNIT CELL DIMENSIONS OF THE SYMMETRICAL HALOGENBENZENES.

By T. BEACALL.

Received 20th May, 1943.

In a previous paper¹ the writer has shown that in the halogenbenzenes the following quantitative relations exist between the melting-points :—

- (1) The introduction of a pair of chlorine (or bromine) atoms in *para*-position increases the melting-point so that the ratio

$$\frac{\text{m.p. of } p\text{-dihalogenated compound}}{\text{m.p. of parent compound}}$$

is approximately constant.

- (2) The introduction of a single asymmetric halogen atom into benzene or a symmetrically-substituted halogenbenzene lowers the melting-point so that the ratio

$$\frac{\text{m.p. of monohalogenated compound}}{\text{m.p. of parent compound}}$$

is approximately constant.

Tables are given in the paper showing that the mean increment in melting-point for a pair of halogen atoms in *para*-position amounts to 1.23 for two chlorine atoms, 1.26 for one chlorine and one bromine atom, and 1.30 for two bromine atoms; for a single asymmetrically substituted halogen atom, the mean decrement is 0.87 for chlorine, 0.90 for bromine, and 0.87 for iodine.

It was suggested that, since the melting-point of a substance is a crystal property, *i.e.* a property of the unit cell rather than of the chemical molecule, each of the two effects stated corresponds with some definite feature

¹ *Recueil*, 1928, 47, 37.

in the unit cells of the series of compounds, and that in the case of the *para*-dihalogen compounds this is probably the linkage in pairs of the halogen atoms of one molecule to those of neighbouring molecules. Reference was made to the work of Plummer,³ whose X-ray investigation of hexachloro- and hexabromobenzene had shown that such an arrangement in fact exists in the unit cells of these two bodies.

In view of the publication since that date of the results of X-ray examination of certain other halogenbenzenes it is now possible to pursue the matter further; the present paper deals with the effect of the replacement of chlorine by bromine upon the melting-points and upon the unit cell dimensions of the symmetrically halogenated benzenes. The melting-point being a crystal property, we should expect some correlation between the change in melting-point and the change in unit cell dimensions when chlorine is replaced by bromine, and this in fact proves to be the case.

From the tables given in the previous paper it is apparent that the mean effect of the replacement of one pair of chlorine atoms in para-position by a pair of bromine atoms is to increase the melting-point in approximately the ratio 1·06.

Plummer's measurements of the unit cell of hexachlorobenzene showed it to be a two-molecular cell with the dimensions $a = 8\cdot10\text{A}$, $b = 3\cdot86\text{A}$, $c = 16\cdot68\text{A}$. $\beta = 116^\circ 52'$. Sufficient measurements of hexabromobenzene were made to show that this likewise has a two-molecule unit cell, whose calculated dimensions are: $a = 8\cdot57\text{A}$, $b = 4\cdot10\text{A}$, $c = 17\cdot6\text{A}$. $\beta = 116^\circ 28\frac{1}{2}'$. Comparison of these measurements for the two hexahalogen compounds gives the following:—

$$\text{ratio of } a \text{ axes} = 8\cdot57/8\cdot10 = 1\cdot058,$$

$$\text{ratio of } b \text{ axes} = 4\cdot10/3\cdot86 = 1\cdot065,$$

$$\text{ratio of } c \text{ axes} = 17\cdot6/16\cdot68 = 1\cdot055.$$

In this pair of compounds, then, the replacement of chlorine by bromine increases each of the axes of the unit cell substantially to the same extent as it increases the melting-point.

So far as the writer is aware, no X-ray measurements of the unit cells of the 1.2.4.5-tetrahalogenbenzenes have been published; since, however, we are concerned here only with the comparative dimensions of the chloro and bromo compounds, we may, without vitiating the argument, arbitrarily assume two-molecule unit cells, and calculate the dimensions of these from the crystallographic data given by Groth;⁴ the calculated dimensions are, for *s*-tetrachlorobenzene, $a = 9\cdot57\text{A}$, $b = 10\cdot59\text{A}$, $c = 3\cdot86\text{A}$, $\beta = 99^\circ 22\frac{1}{2}'$; and for *s*-tetrabromobenzene, $a = 10\cdot40\text{A}$, $b = 10\cdot96\text{A}$, $c = 3\cdot81\text{A}$, $\beta = 94^\circ 24\frac{1}{2}'$. It will be seen that replacement of chlorine by bromine leaves the c axis practically unaffected; the a axis is increased in the ratio 1·085, and the b axis in the ratio 1·035; the joint effect upon the a and b axes is therefore an increase of 1·12, i.e. 1·06.¹ In this case again then, the effect upon unit cell dimensions and upon melting-point is the same.

The unit cells of *para*-dichlorobenzene and *para*-dibromobenzene have been measured by Hendricks⁴; his values for a two-molecule unit cell are:—

p-dichlorobenzene:

$$a = 14\cdot83\text{A}, \quad b = 4\cdot10\text{A}, \quad c = 5\cdot88\text{A}, \quad \beta = 112^\circ 30'.$$

p-dibromobenzene:

$$a = 15\cdot46\text{A}, \quad b = 4\cdot11\text{A}, \quad c = 5\cdot80\text{A}, \quad \beta = 112^\circ 38'.$$

The replacement of chlorine by bromine leaves the b axis unchanged, there is a small decrease in the c axis, and the a axis is increased in the ratio $15\cdot46/14\cdot83 = 1\cdot043$.

In this case, then, the increase in the a axis is materially less than the mean increment of melting-point. It will be observed, however, on

³ Phil. Mag., 1925, 50, 1214.

⁴ Chemische Krystallographie, 4, 7.

⁴ Z. Kristallographie, 1933, 84, 85.

reference to the tables given in the previous paper, that *p*-dichlorobenzene has an abnormally low melting-point, its increment as compared with benzene being only 1.17 as compared with the mean increment of 1.23 for the series of dichlorinated compounds. *p*-Dichlorobenzene thus shows an abnormally low melting-point associated with an abnormally high volume of its unit cell, a feature which was noted in the previous paper in connection with the asymmetric tri- and penta-chloro compounds.

In the related series of *para*-dihalogen nitrobenzenes, the quasi-independent effect upon the melting-point of a pair of halogen atoms in *para*-position persists, and is correlated in the same way with the dimensions of the unit cell; the *p*-dichloro body again shows the phenomenon of abnormally low melting-point associated with abnormally high unit cell dimensions.

The table shows the increment in melting-point of the *p*-dihalogen-nitrobenzenes over that of nitrobenzene, and the corresponding values for

Nitrobenzene Compound.	Melting-Point.	Ratio.	Benzene Compound.	Melting-Point.	Ratio.
Nitrobenzene .	278.7		Benzene .	278.4	
2 : 3-dichlor .	328	1.18	<i>p</i> -dichlor .	326	1.17
2-chlor-5-brom .	345	1.24	<i>p</i> -chlor-brom .	339	1.22
2-brom-5-chlor .	343	1.23			
2 : 5-dibrom .	358.4	1.29	<i>p</i> -dibrom .	360	1.29

the *p*-dihalogenbenzenes. No measurements of the unit cells of the *p*-dihalogen nitrobenzenes appear to have been published; since we are here concerned with comparative dimensions only, we may again make the arbitrary assumption that the unit cells are bimolecular, and calculate the dimensions from the crystallographic data.⁸ The calculated dimensions are:—

2 : 5-dichloronitrobenzene :

$$\begin{aligned}a &= 10.15\text{\AA}, \quad b = 7.05\text{\AA}, \quad c = 5.80\text{\AA}, \\ \alpha &= 87^\circ 18', \quad \beta = 114^\circ 17', \quad \gamma = 82^\circ 37\frac{1}{2}'.\end{aligned}$$

2 : 5-dibromonitrobenzene :

$$\begin{aligned}a &= 10.20\text{\AA}, \quad b = 7.36\text{\AA}, \quad c = 5.80\text{\AA}, \\ \alpha &= 87^\circ 29', \quad \beta = 114^\circ 35', \quad \gamma = 83^\circ 27'.\end{aligned}$$

It will be seen that the *a* and *c* axes are virtually unaffected, while the *b* axis is increased in the ratio $7.36/7.05 = 1.044$, which is practically identical with the increment shown by the *a* axis of *p*-dibromobenzene over that of *p*-dichlorobenzene.

Summary and Conclusions.

In the symmetrically-substituted halogenbenzenes, the replacement by bromine of one, two and three pairs of chlorine atoms in *para*-position produces similar effects upon the melting-points and the dimensions of the unit cells. *p*-Dichlorobenzene exhibits an abnormally low melting-point and abnormally high unit cell dimensions. Similar effects are exhibited by the *p*-dihalogen nitrobenzenes.

⁸ *Chemische Krystallographie*, 4, 44.

THE EQUILIBRIUM BETWEEN LENS AND UNILAYER IN THE SYSTEM HYDROCARBON OIL-OLEIC ACID-WATER, IN RELATION TO THE INTERFACIAL FILM.

BY E. HEYMANN AND A. YOFFE.

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1.

Non-polymerised spreaders, such as oleic acid, etc., never produce stable thick films of hydrocarbon oils on water, but the systems finally revert to lenses in equilibrium with a unilayer.¹ The final spreading coefficient in these systems is always negative.¹ This fact appears to be related to the reduced lateral adhesion between the hydrocarbon chains of the spreader film in the interface as a consequence of the presence of the oil phase, interfacial films generally being more expanded than the corresponding surface films.² Fig. 1 shows this for the interfacial and surface films of oleic acid; F_1 the interfacial pressure (curve 1), and F the surface pressure (curve 2) being plotted against A the area per molecule. However, at high pressures, but below the collapse pressure of the surface film, the curves for the interfacial and surface films approach each other closely, showing that under strong compression both films possess approximately the same density of packing (*cf.* similar observations with interfacial films of oil-insoluble substances by Alexander³).

Table I. shows the variation of $K_F = F_1/F$ with the spreader concentration in the oil phase (c in g. per 100 g.), when a lens of paraffin oil, containing oleic acid, is in equilibrium with a surface film of oleic acid. Although at

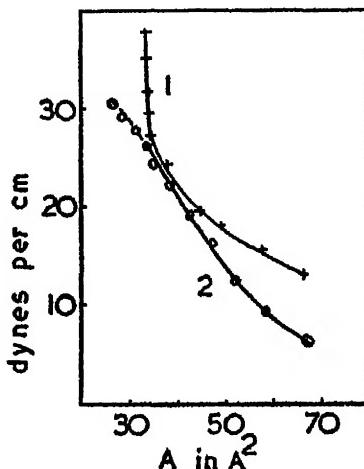


FIG. 1.

TABLE I.

a	F_1	F	K_F
0.1	21.0	6.0	3.50
0.2	24.2	10.0	2.42
0.4	27.4	15.5	1.77
0.6	29.6	19.2	1.54
0.8	31.3	21.2	1.48
1.0	32.6	22.2	1.47
1.6	35.6	25.5	1.40

¹ E. Heymann and A. Yoffe, *Trans. Faraday Soc.*, 1942, 38, 408.

² Literature *vide* N. K. Adam, *Physics and Chemistry of Surfaces*, 3rd ed.

³ A. E. Alexander, *Trans. Faraday Soc.*, 1941, 37, 117.

resultant attraction between the spreader molecules is smaller in the interface than in the surface.

The data for F , F_i and A are calculated from the measurements described previously; ¹ $F = \gamma_w - \gamma'_w$ and $F_i = \gamma_{ow} - \gamma'_{ow}$, where γ_w (γ_{ow}) denote the surface (interfacial) tensions in the pure oil-water system, and γ'_w (γ'_{ow}) those in the systems containing oleic acid. In the case of the interfacial film, A is calculated by the Gibbs equation, assuming that oleic acid exists as double molecules in the paraffin oil phase, as shown previously,^{1*} but A is expressed, as usual, per single molecule. The values for A are somewhat approximate, because of the simplifications involved in the application of the Gibbs equation (2) and since no activity correction can be made because of the lack of data.

2.

When a drop of hydrocarbon oil, containing oleic acid, is placed on a water surface, the oil will spread at first to an extended lens or multi-molecular film. At some stage, however, spreader molecules are shed into the free water surface.⁴ The linear lens boundary acts as an energy barrier, and only molecules possessing a sufficiently high energy may break through that boundary and escape from the interface. The number of molecules (n) possessing a sufficiently high energy may be written as

$$n = n_0 e^{-\frac{f(a_{11}a_{12})}{kT}},$$

where n_0 is the total number of spreader molecules in the interface. $f(a_{11}a_{12})$ is an energy term depending on (a) the forces between the oleic acid molecules (a_{11}), and (b) those between oleic acid and hydrocarbon molecules (a_{12}).

At very low concentrations in the interface, F_i is small, and hence the amount shed is small. Both surface and interfacial films are gaseous, and the influence of the a_{11} forces will be negligible. Hence the distribution

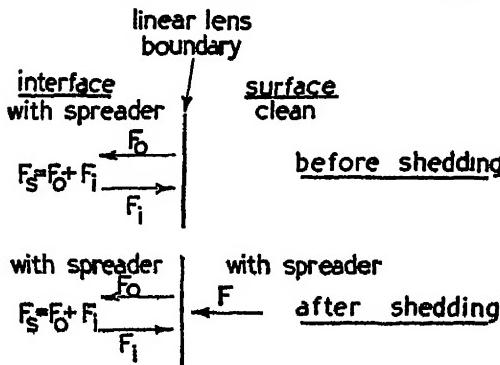


FIG. 2.

of the spreader between interface and surface will be, in the first place, determined by the a_{12} forces, i.e. K_F is large because of the solubility effect of the hydrocarbon oil. With increasing concentration in the interface and surface, however, the a_{11} forces, acting both in surface and interface, will make themselves increasingly felt and F and F_i will tend to approach each other. This is borne out by the experiments (Table I.).

Fig. 2 represents diagrammatically the conditions at the linear lens boundary. F_o is the contracting force (acting on the linear boundary) of the oil lens not containing any spreader, and identical with the spreading coefficient of the oil on water. F_s , the initial spreading coefficient, is the spreading pressure of the lens, i.e. the two-dimensional pressure above that required to counteract the contracting force of the pure oil lens. Hence $F_s = F_o + F_i$ (Langmuir).⁵ Whilst the lens expands to a thick

* Langmuir (*J. Franklin Inst.*, 1934, 218, 166) has shown the same for solutions of stearic acid in tetradecane.

⁴ E. Mercer, *Proc. Physic. Soc.*, 1939, 51, 561.

⁵ I. Langmuir, *J. Chem. Physics*, 1933, 1, 756.

film, $F_s > F$, though F will gradually increase as a consequence of shedding, and of the expansion of the oil lens. During this process, F_s will decrease only slightly (at medium spreader concentrations) because molecules, shed to the water surface, will be replaced from the bulk of the solution.

When F has become equal to F_s , the system is not yet in equilibrium. At the state $F_s = F$, the number of molecules in the interface, having a kinetic energy sufficient to break through the linear boundary, will be greater than the number of such molecules in the surface. This is due to the fact, mentioned previously, that the attraction between the spreader molecules in the surface (determined by a_{11} only) is greater than the resultant attraction between the spreader molecules in the interface (determined by a_{11} and a_{12} , the latter reducing the lateral adhesion between the hydrocarbon chains of the spreader molecules). As a consequence, shedding will continue and F will become greater than F_s , until the number of molecules passing the linear boundary, in both directions is equal. Since $F > F_s$, the thick film will be pushed back to form a lens of such dimensions that the gravity term becomes equal to $F - F_s$, and the final spreading coefficient $F' = F_s - F$ is negative.

Summary.

The final spreading coefficient of hydrocarbon oil, containing oleic acid as a spreader, on water is negative. It is suggested that this is related to the fact that the lateral adhesion between the spreader molecules is smaller in the interface than in the surface. The relation between surface and interfacial pressure, when a lens of hydrocarbon oil containing oleic acid is in equilibrium with a surface film of oleic acid, is discussed.

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THE ACTION OF LIGHT ON ACETALDEHYDE VAPOUR.

By C. W. WOOLGAR * AND A. J. ALLMAND.

Received 27th May, 1943.

The work described below was carried out between January, 1932, and June, 1933. The paper of Leighton and Blacet¹ on the photolysis of propionaldehyde appeared during its course, and their work on acetaldehyde² just as our experiments had to be concluded. Since then a number of other papers have been published, of which it seems unnecessary to give a complete list. The majority of our results are in substantial agreement with these subsequent findings. In some cases, however, they differ in detail or cover rather different ground and, for these reasons, publication seems justified.

The quartz insulation cell (9.7 cm. long, 5.1 cm. diameter) was connected by a graded quartz-glass seal to the remainder of the constant-volume reaction system. Two different sets-up were used, depending on whether quantum efficiencies were being measured or not. In each case, the apparatus was, in general, of the type described by Leighton and Blacet,¹

* Killed on active service in September, 1941, whilst piloting a night fighter over his native Sussex Downs.

¹ *J. Amer. Chem. Soc.*, 1932, 54, 3165.

² *Ibid.*, 1933, 55, 1766.

and included a supply bulb for acetaldehyde, a direct reading mercury manometer with one limb evacuated, a freezing-out bulb immersed when necessary in liquid oxygen, and provision for evacuation and for pumping off the products for analysis. Except for this last purpose, mercury seals were used throughout, to the exclusion of taps. The majority of runs were carried out at 25° C., a few measurements being done at 200° C. In the earlier experiments (series A), the outlying connecting tubes were at room temperature, under which conditions separation of a liquid polymer was noted. This was avoided in the later work (series B—quantum efficiency measurements) by using auxiliary electrical heaters.

The gaseous reaction products were analysed by a modified Bone and Wheeler apparatus, unreacted acetaldehyde being removed by saturated KHSO_4 solution, carbon monoxide by acid Cu_2Cl_3 , and hydrogen and methane being determined in the residue by explosion. The presence of ethane was tested for by the method of Walker and Shukla; ³ none was ever detected with any certainty, in agreement with later published results. Unsaturated hydrocarbons were absent. The water-white liquid product had a vapour pressure of 0.99 cm. at 16° C., as against 1.02 cm. (2.83 cm. at 25°) given by a specimen of paraldehyde. We assumed the latter to be the polymerisation product. The washings from the cell after reaction contained no trace of acid. Tests for diacetyl, glyoxal and formaldehyde, found in later work,⁴ were not applied.

All experiments were carried out with filtered light from a quartz-mercury arc. Three filters were used, *viz.* (i) Cl_2 gas, (ii) a $\text{Cl}_2\text{-Br}_2$ filter with an excess of liquid Br_2 , (iii) 0.5 cm. of 0.003 molar K_2CrO_4 plus 0.01 molar KOH. The spectral distribution of the transmitted energy was determined at various periods during the work, using a large quartz monochromator and thermopile. On the basis of quanta incident on the reaction cell, the most intense transmitted lines in the ultraviolet were respectively 2537, 2654 and 3130 Å. When quantum efficiencies were being measured (series B), the incident light was much less intense than in series A. A parallel beam, very nearly filling the cross-section of the cell, was employed, subsequently concentrated on to a 2-cm. surface thermopile, calibrated by means of standard metal filament lamps. Owing to the relatively small proportion of ultra-violet light in the incident beams (11-19 %) it was impracticable to measure the absorbed energy directly. This was instead calculated from the thermopile readings obtained (a) with the cell empty, with and without the interposition of a thick glass plate, and (b) with the cell filled, at various stages during the run. These data were combined with the measured spectral distribution of the filtered light used and the known extinction coefficients of acetaldehyde vapour, the relevant reflection corrections being applied in all cases.

In what follows, the following aspects of the experiments will be discussed . . . ; (a) the results of the gas analyses, (b) the pressure changes during insolation, (c) the quantum efficiencies.

The Composition of the Gaseous Products of Reaction.

The results considered were all obtained during series A, when considerable quantities of gas were available for analysis. The amounts obtained during a 24-hour run in series B were of the order of 1 c.c., and only the figures for CO, agreeing with those recorded below, can be looked on as sufficiently reliable. Typical figures are contained in Table I.

The data are in qualitative agreement with those published in recent years. Thus, at 25°, the ratio H_2/CO decreases with increasing λ , but more rapidly than was found by Blacet and Volman.⁵ The ratios of CH_4/CO

³ *J. Chem. Soc.*, 1931, 368.

⁴ Blacet and Blaedel, *J. Amer. Chem. Soc.*, 1940, 62, 3374.

⁵ *Ibid.*, 1938, 60, 1243.

are appreciably higher than those quoted by Blacet and Blaedel,⁴ whilst decreasing slightly with decreasing λ . The percentage of CO in the products of photolysis at 200° is rather higher than that reported either by Leermakers⁶ for 300° or by Rollefson and Grahame^{7,8} for 100°-350°, whilst the proportion of hydrogen, although lower than at room temperature, is considerably higher than would correspond to the results of Blacet and Volman.⁵

It has been suggested in the past that photolysis of the polymerised product may have been the cause of discrepancies between the analytical results of different workers on this reaction. We found that 24 hours insulation at 25° of the cell containing saturated paraldehyde vapour (2.83 cm.), using Cl₂-filtered light, gave no pressure change exceeding the experimental error (0.01 cm.). This is in accordance with the very low

TABLE I.

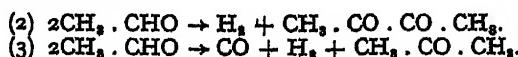
No.	Filter.	Initial P(cm.)	Temp. (°C.)	Percentage of			Ratio of			
				CO.	CH ₄ .	H ₂ .	CH ₄ /CO.	H ₂ /CO.	C/O.	H/O.
A. 4	Cl ₂ -Br ₂	37.90	25	48.2	47.8	4.0	0.99	0.083	1.99	4.14
A. 5	Cl ₂ -Br ₂	30.43	25	48.05	47.2	4.75	0.98	0.098	1.98	4.13
A. 9	Cl ₂	33.78	25	46.6	44.2	9.2	0.95	0.195	1.95	4.18
A. 12	Cl ₂	20.97	200	49.8	46.5	3.7	0.93	0.074	1.93	3.88
A. 15	Cl ₂	34.00	200	49.1	46.0	3.9	0.96	0.080	1.96	3.98
A. 14	Cl ₂	57.75	200	49.5	47.7	2.8	0.96	0.057	1.96	3.97

extinction coefficient of paraldehyde in this region.⁹ 1.03 cm. of the vapour was then introduced into the apparatus at 200°. There was no detectable pressure change in 1½ hours. Insolation was commenced and continued for 65 hours. During this time, the pressure rose to 3.53 cm., falling to 3.13 cm. on application of liquid oxygen to the freezing-out tube. The gases were not further examined but, taking into account the low extinction of paraldehyde just referred to, it seems highly probable that the controlling reaction was the slow thermal depolymerisation of the vapour,¹⁰ followed by photolysis of the monomer.

The ratios in the last two columns of Table I deviate from the respective values of 2 and 4 which they would have if the gases consisted of nothing but equal proportions of CO and CH₄. No obvious sign of any solid product was noticed on the inside of the cell, nor did its transmission, when empty, alter as the result of an experiment. The liquid product, after pumping out, had a vapour pressure very slightly lower than that of pure paraldehyde. No C₂H₆ was found in the gases. The obvious conclusion is that the deviations from the 1 : 1 :: CO : CH₄ ratio are bound up with the formation of small quantities of liquid products which probably dissolve in the polymer during the course of the run. The simplest explanation is to suppose the simultaneous occurrence with the main reaction



of the two *overall* reactions.



⁶ *J. Amer. Chem. Soc.*, 1934, 56, 1537.

⁷ Rollefson and Grahame, *J. Chem. Physics*, 1939, 7, 775.

⁸ Grahame and Rollefson, *ibid.*, 1940, 8, 98.

⁹ *I.C.T.*, 5, 365.

¹⁰ Coffin, *Canad. J. Res.*, 1932, 7, 75; 1934, 11, 180.

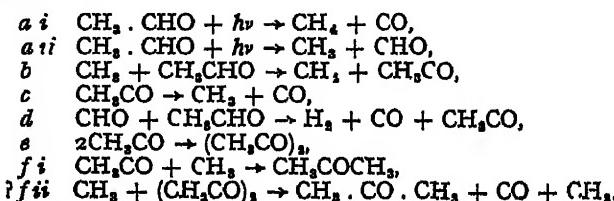
In Table II, the data for three of the experiments of Table I are expressed on this basis, the figures in the numbered columns giving the percentages of acetaldehyde molecules which will have undergone decomposition in accordance with the three different schemes.

TABLE II.

No.	Filter.	Temp.	$\text{CH}_3 + \text{CO}$.	(2) Diacetyl + H_2 .	(3) Acetone + CO + H_2 .
A. 4	Cl-Br ₂	25°	85.7	12.9	1.4
A. 9	Cl ₂	25°	70.6	21.7	7.7
A. 12	Cl ₂	200°	86.3	1.5	12.2

Since the work of Barak and Style¹¹ and of Spence and Wild,¹² it has generally been agreed that diacetyl will be the product of an important chain-ending reaction in this photolysis, and recently Blacet and Blaedel¹ have published the results of experiments in which they have detected and measured the amounts produced, not only of diacetyl, but also of glyoxal and formaldehyde. Neither methyl-glyoxal nor acetone was found. Their experimental conditions did not, however, correspond with ours. Long-continued exposure to the full light of a mercury arc was used, "considerable resinous material" collected on the walls of the tube, and no liquid, but a solid, polymer of acetaldehyde was produced. The possible formation of acetone as a product of acetaldehyde photolysis under other experimental conditions cannot then be said to have been disproved, and, in the absence of ethane, it is difficult to see how any other simple explanation can be given of the fact, generally agreed on, that more CO than CH_4 is produced in the reaction. The ready occurrence of the process $\text{CH}_3 + \text{COCH}_3 \rightarrow \text{CH}_3 \cdot \text{CO} \cdot \text{CH}_3$, as a homogeneous gas phase reaction is regarded by Herr and Noyes¹³ as necessary to explain the facts of acetone vapour photolysis in the near ultra-violet.

The following steps are involved in the three overall equations under consideration:



(1) is concerned with *a i*, *b* and *c*, (2) with *a ii*, *b*, *d* and *e*, and (3) with *a ii*, *d* and *f ii*—or possibly with *a ii*, *b*, *d*, *e* and *f ii*.

Turning back to Table II, the greater relative importance of equations (2) and (3) in A. 9 than in A. 4 suggests that the excess of energy contained in the primarily formed CHO radicals may assist in step *d*, and that possibly this may also be true of CH_3 radicals in respect of step *f ii*. The former suggestion is not a new one (Gorin;¹⁴ Blacet and Volman¹⁵). The greater importance of (1) at high temperatures (*cf.* A. 9 and A. 12) is concerned with step *c*. The effect of temperature on the relative parts played by schemes (2) and (3) is rather striking (A. 9, A. 12). A plausible explanation would be that step *f ii*, which requires activation, becomes important at high

¹¹ *Nature*, 1935, 135, 307.

¹² *J. Chem. Soc.*, 1937, 352.

¹³ *J. Amer. Chem. Soc.*, 1940, 62, 2052.

¹⁴ *Acta Physicochimica U.R.S.S.*, 1938, 9, 681.

temperatures. The analytical data obtained by Anderson and Rollefson¹⁶ in their work on the photolysis of diacetyl suggest the possibility of such a reaction.

The Pressure Changes Measured at the End of the Reaction.

At the end of a run, after reading the final pressure, the freezing-out bulb was immersed in liquid oxygen, and the pressure again measured. It is assumed in the case of series B that the amount of aldehyde decomposed is given by one half of this residual pressure, an approximation which will not affect the main conclusions drawn. Then, if p_0 is the original aldehyde pressure, p_t the final total pressure, p_a the final aldehyde pressure, p_π the pressure of polymer, p_d the pressure of aldehyde decomposed ($2p_d$ being pressure at liquid oxygen temperature), and p_p the pressure of aldehyde polymerised, we have

$$\begin{aligned} p_t &= p_a + p_d + p_p, \\ p_a &= p_t - p_\pi - 2p_d \end{aligned}$$

from which p_p and p_a can be calculated. The results obtained are collected in Table III.

As a result of the relatively low light intensities employed, the proportion of aldehyde disappearing during the insolation was low, some 2·5-10 %. The quantities polymerised at 1 and 5 cm. were too small to be estimated with any certainty, except at 5 cm. pressure when using the K_2CrO_4 filter, and the corresponding experiments are therefore omitted. All runs were at 25° and lasted 20-24 hours. Pressures are given in cm.

TABLE III.

No.	Filter.	p_0 .	p_t .	$2p_d$.	p_d .	p_p .	p_a .	Ratio $p_p : p_d$.
B. 10	Cl ₂	15·13	15·54	0·97	0·49	0·10(5)	14·53(5)	0·21
B. 8 .	Cl ₂	16·16	16·62	1·08	0·54	0·12	15·50	0·22
B. 9 .	Cl ₂	20·36	30·11	1·93	0·96	0·33	28·07	0·34
B. 18 .	Cl ₂ -Br ₂	16·85	16·91	0·50	0·25	0·28(5)	16·31(5)	1·14
B. 20 .	Cl ₂ -Br ₂	29·02	28·96	0·59	0·30	0·52(5)	28·19(5)	1·75
B. 23 .	Cl ₂ -Br ₂	31·78	31·67	0·43	0·23	0·48	31·08	2·18
B. 17 .	K ₂ CrO ₄	5·16	5·24	0·42	0·21	0·195	4·755	0·93
B. 16 .	K ₂ CrO ₄	5·85	5·89	0·39	0·20	0·225	5·425	1·13
B. 11 .	K ₂ CrO ₄	15·64	15·14	0·45	0·23	1·08	14·33	4·70
B. 15 .	K ₂ CrO ₄	17·30	16·56	0·46	0·23	1·455	15·615	6·33
B. 12 ,	K ₂ CrO ₄	20·84	28·23	0·43	0·22	2·79	26·70	9·8
x ₃ , x ₄		-32·05	-30·33	-0·58	-0·29	-2·94	-28·86	-12·7

Apart from what has been said about the runs at 1 and 5 cm., the favourable effect of increased pressure on polymerisation is obvious, as also that of longer wave-length. The actual figures for polymerisation are far higher than the "apparent polymerisations" given by Leighton and Blacet.² These authors have tacitly assumed that the polymer exerts no appreciable vapour pressure, i.e. p_π is taken as zero in the expressions

$$p_t = p_a + 2p_d + p_\pi$$

and

$$p_p = p_d + p_0 - p_t + p_\pi.$$

No actual pressure measurements are quoted in their paper.

In series A intensities were higher, of the order of 20-50 times those in series B and, during the usual run of about 24 hours, at least 80 % of the

original aldehyde was decomposed or polymerised. The same experimental procedure, *viz.* measurement of the pressure after the conclusion of a run after immersion of the freezing-out bulb in liquid oxygen, was also applied in these experiments, but, owing to the facts (1) that the pressure of CH_4 developed exceeded the saturation vapour pressure of liquid methane at liquid oxygen temperature (about 8.3 cm.), and (2) that this gas condensed out very slowly, no quantitative deductions can be drawn from the results. If the actual pressure readings noted after the first rapid condensation had ceased (20-80 cm., depending on the experimental conditions during isolation) can be looked on, which seems probable, as corresponding to negligible or small CH_4 condensation, then the results of the experiments agree with those of series B, in that both high aldehyde pressure and longer wave-length favour polymerisation relatively to decomposition. They also show clearly that, at 200°C., the $p_p : p_d$ ratio falls considerably, although polymerisation when using Cl_2 -filtered light is still marked (compare⁷ and⁸).

Quantum Efficiencies.

For various reasons, the measurements with the two bands of shorter wave-length were not very satisfactory. The data with the 3130-3022 Å. light were far more reliable. The intensities were a good deal more constant and also higher, particularly when compared with the $\text{Cl}_2\text{-Br}_2$ filtered light. The results are contained in Table IV.

TABLE IV.

No.	(a) Cl_2 Filter.			No.	(b) $\text{Cl}_2\text{-Br}_2$ Filter.			No.	(c) K_4CrO_4 Filter.		
	Initial Pressure (cm.)	γ_D	γ_P		Initial Pressure (cm.)	γ_D	γ_P		Initial Pressure (cm.)	γ_D	γ_P
B. 7	1.25	0.80	—	B. 22	5.71	0.49	—	B. 17	5.16	0.31	0.29
B. 3	4.90	1.11	—	B. 21	6.18	0.54	—	B. 16	5.85	0.32	0.36
B. 4	4.98	1.11	—	B. 18	16.85	0.76	0.87	B. 11	15.64	0.20	1.22
B. 10	15.13	0.86	0.18	B. 20	29.02	0.66	1.10	B. 15	17.30	0.21	1.33
B. 8	16.16	0.78	0.17	—	—	—	—	B. 14	29.84	0.23	2.26
B. 9	29.36	1.01	0.34	—	—	—	—	B. 12	31.31	0.20	2.54
—	—	—	—	—	—	—	—	B. 13	32.05	0.24	2.83

The values of γ_D are based on the assumption, only approximate but generally adopted, that CO and CH_4 in equal quantities are the sole decomposition products. The figures for γ_P , which refer to molecules of acetaldehyde, not of polymer, are obtained from γ_D by multiplying by the ratios in the last column of Table III.

The values of γ_D for the regions 2537-2654 Å. (Table IV(a)) and 2654-2804 Å. (Table IV(b)), are in general accord with the results of Leighton and Blacet,⁹ whose incident intensities, expressed as ergs/second, were respectively about twice and three times our figures. The values for the region 3130 (3022) Å. are in much closer agreement, particularly if the fact is taken into account that our incident intensities were only 5500-6600 ergs/second, or about 25-30 % of the intensities used in the majority of their experiments. It may be noted that they found γ_D , at a given intensity, to rise with fall in aldehyde pressure, whilst our highest values were also obtained with the lowest aldehyde pressures used.

Attention has already been drawn to the relatively high degrees of polymerisation observed in our work. These are in agreement with the

earlier experiments of Bowen and Watts,¹⁶ who found, after a necessary correction has been applied to their figures,² γ_D for saturated, and γ_P for unsaturated vapour, to be respectively about 0.22 and 0.88 with light of 3130 Å. The data of Table IV (*a*) and (*c*) are concordant with the work of Gorin.¹⁴ As, however, some important aspects of his results have recently been questioned,^{17, 18} no further discussion will be attempted.

Summary.

The behaviour of acetaldehyde in ultra-violet light has been examined, the proportion of the starting material undergoing reaction being considerably higher than in quantitative studies reported during recent years. Large quantities of a liquid polymer, in all probability paraldehyde, are produced, the relative degrees of decomposition and polymerisation depending on the experimental conditions. There were no complications arising from subsequent decomposition of the polymer.

The analyses of the gaseous products of photolysis, which are in general agreement with those of other workers, lead to the conclusion that the only simple explanation of the data involves the formation of acetone as a reaction product.

Quantum efficiency measurements are briefly reported. Those for the decomposition agree, within the limits of experimental error (sometimes considerable) with the results of Leighton and Blacet. Those for the polymerisation are more detailed than any others hitherto published.

The junior author would have wished to acknowledge the receipt of a maintenance grant from the Department of Scientific and Industrial Research, which enabled him to engage in this work.

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¹⁶ *J. Chem. Soc.*, 1926, 128, 1607.

¹⁷ Blacet and Heldman, *J. Amer. Chem. Soc.*, 1942, 64, 889.

¹⁸ Blacet and Loeffler, *ibid.*, 893.

REVIEWS OF BOOKS

Principles and Practice of Chromatography. By L. ZECHMEISTER and I. CHOLNOKY. Translated from the second and enlarged German edition by A. L. BACHARACH and F. A. ROBINSON, with a foreword by I. M. HEILBRON. (London: Chapman & Hall, 1943.) Pp. xv + 378. Price 25s. net. Second impression.

The reprinting, after two years, of Zechmeister and Cholnoky's book is in itself proof of the great and still increasing importance of chromatography both as an analytical and a preparative procedure. It is no exaggeration to say that to-day chromatographic adsorption methods are used in some form by the large majority of organic chemists; these will find Zechmeister and Cholnoky's monograph an invaluable adjunct in their work.

The introductory portion of the book, containing a discussion of the theoretical aspects of chromatography, is particularly important and exceptionally well documented by references to the original literature. The book is thus not merely a guide for the practical organic chemist

who uses the method more or less empirically, but contains a discussion of the many problems still awaiting solution. This is of particular interest to the physical chemist, to whom the subject must afford a wide field of inquiry.

The translators are to be congratulated on having added to the present edition a supplement containing over 300 additional references covering the period 1938-1941. This constitutes a valuable guide to a rapidly growing branch of chemical literature, even though it is not claimed to be complete.

G. A. R. K.

High Polymers : Vol. IV. "Natural and Synthetic High Polymers, a Textbook and Reference Book for Chemists and Biologists."
By KURT H. MEYER, translated by L. E. R. PICKEN. Interscience Publishers, Inc. New York, 1942. Pp. 690 + xviii. Price eleven dollars.

This volume, bringing up-to-date the systematic part of the important pioneer book by Meyer and Mark, *Die Aufbau der hochpolymeren Substanzen*, 1930, is a masterly and many-sided work, likely to remain the standard textbook in its field for many years to come. It begins with a general account of the principles and methods of investigation suitable for high polymers, and then proceeds to a systematic description of all the principal types of polymers known. First come inorganic polymers of many kinds; next, 130 pages on rubber and synthetic organic polymers of practically all kinds; complex carbohydrates occupy the next 200 pages, the sections on cellulose and the complex substances which accompany it in nature being exceptionally complete and informative; in the next 140 pages, although the author confesses himself unable to deal with proteins to his own satisfaction, he contrives to give a perfectly balanced and very readable account of most of their important properties, and many will find this one of the best accounts of proteins, especially in their physico-chemical aspects insofar as these can be linked with their chemical constitution, to be found anywhere at the present time. This chapter concludes with a short account of viruses. Finally, there are less complete sections on surface films, membranes and their permeability, bio-electric phenomena; and one, probably intended as an introduction to a much wider and only slightly explored field, deals with the molecular structure of animal and plant tissues.

Not only are almost all properties of high polymers very ably and concisely reviewed, but also the author continually shows how the macroscopic physical and mechanical, as well as chemical, properties depend on the chemical constitution of the substances which are polymerised. For the first time, perhaps, the importance of what may be termed "chemical morphology," the organisation of structures composed of units of known chemical properties, is clearly and comprehensively set before the reader. The book is a model of what a modern textbook of organic chemistry should be, but alas! so seldom is. The author is a master of the classical chemical technique of organic chemistry, whose principles were so thoroughly worked out in the latter half of the nineteenth century, but he properly discards all conventional distinctions between "organic"

and "physical" chemistry, and marshals with consummate generalship organic chemical technique, X-ray diffraction, electron microscopy, optical and thermal investigations, and all the usual physico-chemical methods applicable to solutions, to elucidate the molecular constitution of these complex substances; and the whole is brought clearly into relation with the mechanical properties. As might be expected from one who has held a very important position in chemical industry, the industrial aspects of high polymers are treated in considerable detail, although this is primarily a scientific, not an industrial, textbook.

The book may prove to be one of the really great textbooks of chemistry. One is tempted to compare it with Meyer and Jacobson's *Organic Chemistry*. Its style is less spacious and leisurely, and it does not, of course, cover all types of organic compounds. It does, however, focus on a most important group of compounds a wide range of methods of investigation, many of which were unknown when the earlier great textbooks of organic chemistry were written. It is no less readable than Meyer and Jacobson, and scarcely less thorough and well-balanced. As the title indicates, it is intended for chemists and biologists—one might add, also, for progressive industrialists. The relation between chemical constitution and physical properties, of a useful kind, which depend on structural organisation of large numbers of molecules, is a branch of chemistry hitherto rather neglected, but it is of immense importance to biology and to industry.

The reviewer has very few criticisms; a purist would probably criticise the thermodynamic reasoning on pp. 149-55, but the final formulae for the thermo-elastic effect appear correct, and the subsequent explanation of this effect in terms of quite easily visualised probabilities of the arrangement of molecules is an unusually clear exposition, qualitatively, of what entropy can mean in terms of organic molecules. A very few sections are a little sketchy, but these are not part of the main plan of the book.

The author is a great German chemist, for whom his country, we may hope only temporarily, had no further use after 1932. The translator, who has done his work so well that no one would guess the present volume was a translation, is in Cambridge, England; and the editing and printing, also of the highest quality, are from America. If this volume could be taken as an indication of what we may expect in international co-operation after the war, there need be no fear as to the future of the post-war world.

N. K. A.

Schmidt's Organic Chemistry. Fourth English Edition by H. GORDON RULE. Gurney & Jackson, London. Pp. xxvii + 923. Price 28s. net.)

Dr. Gordon Rule was able to send the manuscript of this book to the printer before he was overtaken by fatal illness. The revision and the choice of new matter was done with that thoroughness and competence which was characteristic of him.

Schmidt has established itself as a book of reference particularly suitable for those whose daily work only touches organic chemistry to a lesser extent. It is entitled a text-book but it is more than that. The text is so full and so adequately annotated and indexed that it can be used as a book of reference. A particularly useful feature of the annotation is the inclusion of references to fuller works where the subject can be

studied. By way of example, a new Chapter XIII of Part III deals with Synthetic Resins ; it quite properly only occupies 10 pages but the reader is referred to this Society's 1935 General Discussion and to other work.

It should be unnecessary to detail the general outlines of the book. The same lay-out as in previous editions is maintained ; Part I Aliphatic, Part II Carbocyclic, Part III Heterocyclic. New matter deals with the electronic theory of benzene substitution (as an addition to Part II, Chapter II, Introduction to the Aromatic Series), Robinson's theory of phytosynthesis of the alkaloids (summarised in about 2 pages) and resonance (which in 1936 received only passing mention and now occupies 6 pages). The 4 pages dealing with rubber now more logically come in Chapter XII, Part II, following the terpenes, and are followed by 3 pages on synthetic rubber. Four pages are added to Chapter XIV, Part II, to deal with strainless rings and condensed ring structures. A new chapter (XVIII) is added to summarise present knowledge on the steroids and sex hormones, which received scant attention in 1936 and were then found in the last chapter dealing with vitamins and enzymes. Other new chapters deal with recent developments in chemotherapy and deuterium compounds.

Dr. Neil Campbell, who saw the work through the press on the death of the author, has devoted great care to his task ; misprints are rare and one appreciates how readily organic formulæ lead to difficulty with printers. The publishers are to be congratulated on the production and binding which are "pre-war" ; the price is reasonable.

THE SURFACE TENSION OF WHITE PHOSPHORUS.

BY E. HUTCHINSON.

Received 31st May, 1943.

1. The Surface Tension of White Phosphorus.

The only value to be found in the literature for this quantity is that given by Ramsay.¹ This value must be discounted as, on that author's admission, the contact angle of phosphorus against glass, though observed not to be zero, was not measured but was assumed zero for the calculation.

Experimental Method.

The Sugden Maximum Bubble Pressure Method was used as this method obviates the need for measuring the contact angle. The apparatus used was that described by Sugden² with the following modifications:—

1. The gas (CO_2) was blown through the molten phosphorus as this afforded better rates of bubbling.

2. A Bourdon gauge was used to measure the pressure difference instead of the alcohol manometer used by Sugden. This was necessary because the whole apparatus had to be evacuated to remove oxygen. The gauge was calibrated against a mercury manometer.

The phosphorus used in these experiments was kindly supplied and very carefully purified by Mr. G. Inglis of Messrs. Albright and Wilson Ltd., Birmingham. Sulphur, lead, iron, and organic matter were absent, and arsenic was present in less than 20 parts per million.

The CO_2 used for bubbling was freed from oxygen by bubbling through molten phosphorus before being admitted to the apparatus.

Having introduced the CO_2 , bubbles were blown in the molten phosphorus and the pressure difference across the two sides of the bubble measured directly on the Bourdon gauge.

Results.

The apparatus was calibrated against a number of organic liquids and the mean calibration used. Table I gives a list of the liquids used for

TABLE I

Liquid.	Temp. °C.	γ obv'd. dynes/cm.	I.C.T. value dynes/cm.
Chlorobenzene .	18.0	Used as initial calibrant	
Chloroform .	18.0	27.31	27.36
Diethyl ether .	18.0	16.70	16.79
Methyl alcohol .	18.0	22.33	22.43
Acetone .	18.0	23.10	23.83

¹ Sir W. Ramsay, *J.C.S.*, 1894, 64, 172.

² S. Sugden, *ibid.*, 1922, 121, 858.

the calibration. Table II gives the results obtained for phosphorus calculated from the equation :—

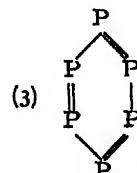
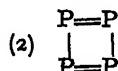
$$Y = 1.224 \times dp \left(1 + \frac{0.138\rho}{dp/981} \right) \quad . \quad . \quad . \quad (1)$$

TABLE II

Temp. °C.	γ dynes/cm.
50.0	69.70
54.0	68.53
60.2	66.95
68.7	64.95

where dp = pressure difference in
dynes/sq. cm.
and ρ = density of phosphorus.

The observed parachor of atomic phosphorus as calculated from these results is 51.2. To obtain the true parachor something must be known of the molecular composition of the molten phosphorus. The following structures may be proposed for the polymerised molecule—



The true parachor can then be evaluated as

$$\begin{aligned} (1) [P]_{obs} &= 102.4 & \text{Treble bond} &= 46.6 & \therefore [P](\text{atomic}) &= 27.9. \\ (2) [P]_{obs} &= 204.8 & 2 \text{ double bonds} &= 46.4 \\ & & 4 \text{ membered ring} &= 11.6 \\ & & \therefore [P]_{\text{atomic}} &= 36.7. \\ (3) [P]_{obs} &= 307.2 & 3 \text{ double bonds} &= 69.6 \\ & & 6 \text{ membered ring} &= 6.1 \\ & & \therefore [P]_{\text{atomic}} &= 38.6. \end{aligned}$$

The value for the atomic parachor of phosphorus quoted by Sugden and calculated from the parachors of various phosphorus compounds is 37.7: this is intermediate between the values for structures 2 and 3. Structure 1 would therefore appear to be unlikely, whereas structures 2 and 3 may well represent the constitution of molten phosphorus.

The Eötvos constant of phosphorus as calculated from the author's data is 1.38, which, when interpreted on a basis of molecularity, yields a value of 2. It is known that the association in phosphorus is much higher than this, e.g. P_4 , P_8 . If any meaning is to be attached to the molecularity obtained in this way it may imply that of the various polymers present in molten phosphorus the P_8 molecule is the most surface-active species.

2. On the Measurement of Interfacial Tension.

There has long been felt the need for an accurate and rapid method of measuring interfacial tension. There are several methods available but they all suffer either from limited applicability or from difficulty in operation. The most generally used and probably the most accurate is the drop-volume method,⁸ but it is tedious in view of the exacting conditions required for the formation of the drop and the care needed in the preparation of the tip of the dropping tube. Small variations in the rate of bubbling lead to quite considerable error and the method also involves the tedious calculation of the appropriate correction constant. When only small quantities of material are available the micro-method

⁸ Harkins and Brown, *J.A.C.S.*, 1919, 41, 499.

similar to that used by Adam⁴ for surface tensions can be used. Although the method gives accurate results, it is unsuitable for rapid routine determinations. The ripple method⁵ has been applied to interfacial measurements but with no outstanding success; this method which is only quasidynamic requires a large interface which is difficult to keep clean.

The ring method⁶ as applied to interfaces promised to be a very accurate and rapid method but it is limited in applicability. For the determination to be at all possible the ring must be completely wetted by the lower liquid; this condition is not satisfied by many liquid-liquid systems. The method is very good where applicable and is one of the few methods available for interface at which insoluble films are being spread and at which time-factors enter into account.⁷

Various methods have been proposed which involve the principle of capillary rise.^{8, 9, 10} All these, however, involve a knowledge of the interfacial contact angle, and although in all cases of data obtained by such methods this angle is observed, or assumed, to be zero, this is not always the case.

The difficulty of measuring contact angles is at least as great at the liquid-liquid interfaces as at the gas-liquid interface so that if the contact angle is not zero the method involves considerable labour and, probably, considerable error.

An attempt has therefore been made to modify the Sieden Maximum Bubble Pressure Method¹ for use at liquid-liquid interfaces, as this method is independent of contact angles. The problem was purely a practical one as the theory of blowing bubbles of one liquid inside another is the same as that for blowing bubbles of gas inside a liquid.

Experimental Method.

The apparatus is shown in Fig. 2. It consists of a tube T diam. c. 4 mm. sealed

⁴ N. K. Adam, *The Physics and Chemistry of Surfaces* (Oxford University Press, 1938), p. 379.

⁵ Watson, *Physical Review*, 1901, 12, 257.

⁶ Harkins and Jordan, 6th Colloid Symposium Monograph, 1929, p. 39.

⁷ Alexander and Teorell, *Trans. Faraday Soc.*, 1939, 35, 727.

⁸ Reynolds, *J.C.S.*, 1921, 119, 460.

⁹ Bartell and Mack, *J. Amer. Chem. Soc.*, 1932, 54, 936.

¹⁰ Speakman, *J.C.S.*, 1933, 150, 1449.

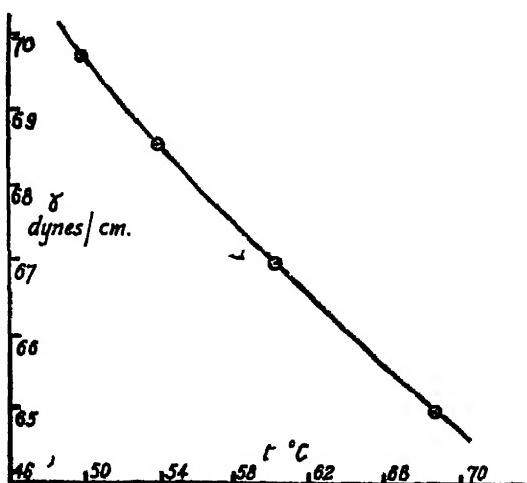


FIG. 1.

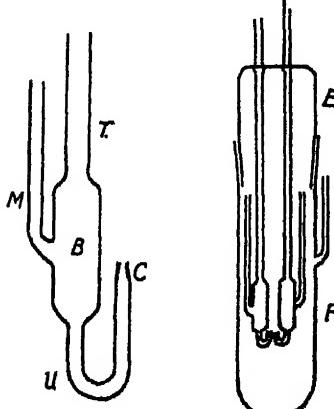


FIG. 2.

on to a bulb B, to which is also sealed a side tube M and a U-tube U which is drawn off to a capillary C. Two such bubblers, differing only in the size of the capillary tip, are sealed into the wide tube E (Fig. 2) which fits into a tube F by means of a ground joint, in such a way that when the apparatus is set in a vertical position the two capillary tips are at the same height.

Liquid X is poured into F so as to cover the capillary tips to a height of about 1 cm., and liquid Y is poured down the inside of the tubes T, care being taken that no air bubbles are trapped in the capillaries, until the liquid Y reaches a height about 2-3 cm. up the side tube M. The pressure of the air above the liquid Y in the tubes T is then gradually raised by means of an aspirator and the level of Y in the tube M rises. At a certain critical height h' however the level ceases to rise and then rapidly falls as a bubble of liquid Y is formed inside liquid X and then detaches itself from the capillary tip. By raising the pressure slowly the height h' at which the maximum pressure is reached is readily observed.

All that is required for a determination of the interfacial tension is the difference $(h' - h'')$ of the heights at which the bubble breaks away from the capillaries 1 and 2.

The Sugden approximation formula can be used in the calculation of the interfacial tension:—

$$T = (h' - h'') \cdot g\rho \cdot \left(1 + \frac{0.6r}{\rho \cdot h} \right) \cdot \text{constant} \quad . \quad . \quad (2)$$

where ρ is the density of the liquid Y and r is radius of the wider capillary. The correction term for the apparatus when r = about 0.5 mm. is of the order of 0.2 % so that to this order of accuracy the apparatus is direct reading in that the interfacial tension is proportional to $(h' - h'')$.

It appears to be immaterial whether the liquid X is heavier or lighter than liquid Y.

The apparatus was calibrated against the chlorobenzene-water interface. The values given by the apparatus for various other interfaces are shown in Table III.

TABLE III

System.	Temp. °C.	γ Observed dynes/cm.	I.C.T. value.	
Chloroform-water .	20.0	31.6	32.80	Preliminary rough experiments show that the apparatus yields results of the correct order for mercury-oil systems.
n-Heptane-water .	20.0	50.4	—	
Benzene-water .	20.0	35.1	35.00	
Diethyl ether-water	20.0	10.9	10.70	

to measure the interfacial tension of molten white phosphorus against water and a number of organic liquids. It was found that it was rather better to have the phosphorus in the inner tubes T; the phosphorus was protected against atmospheric oxidation by covering it with the liquid X. The number of readings to be made is thereby increased; the term $(h' - h'')$ in equation 2 is replaced by $(h'_x - h''_x)\rho_x + (h'_p - h''_p)\rho_p$, where h' and h'' refer to the wide and narrow tubes respectively, and ρ_p and ρ_x are respectively the density of phosphorus and the liquid X. By careful filling of the apparatus the term $(h'_p - h''_p)$ can be made very small.

All the liquids used were freed from dissolved oxygen and the phosphorus and liquid X were in all cases mutually saturated.

The density of the various liquids when saturated with phosphorus were measured in order to calculate the interfacial tension. By comparison of these values with the values for the pure liquids the solubility of phosphorus in the various solvents has been calculated. These may,

of course, be inaccurate due to non-additivity of the volumes of solvent and dissolved phosphorus.

Results.

The results obtained with phosphorus and a number of liquids are given in Table IV.

TABLE IV

System.	Temp. °C.	γ Dynes/cm.	Solubility of P gm. moles/litre.	Heat of solution.
Phosphorus-water	40.0	52.90	—	—
	52.8	51.20	—	—
	61.0	49.70	—	—
	64.0	48.10	—	—
P-benzene	71.0	46.7	—	—
	52.0	13.0	0.689	—
	60.0	12.5	0.868	4.97
	67.0	11.5	1.269	4.82
P-cyclohexane	50.0	18.1	0.634	—
	58.0	17.9	0.901	6.04
	69.0	17.2	1.192	8.00
	50.0	23.3	0.978*	—
P-n-hexane	60.0	23.7	0.992*	—
	50.0	29.7	0.573	—
	60.0	27.9	0.686	3.81
	68.0	27.4	0.772	3.32
P-acetone	46.5	29.4	0.238	—
	50.0	29.1	0.385	2.06
	54.0	29.1	—	—
	—	—	—	—

* Probably slightly incorrect.

With so few results it is impossible to arrive at any general conclusions but the values show that, as one might expect, the greater the solubility of the phosphorus in a liquid the lower is the interfacial tension; the results also demonstrate quite clearly the effect of molecular structure on the interfacial tension; e.g. phosphorus has the lowest interfacial tension against benzene. That the double bonds in benzene play a part in the association with the phosphorus is shown by the increase in interfacial tension in passing from benzene to cyclohexane, while the increase in passing from cyclohexane to hexane shows that the cyclic nature of benzene and cyclohexane influence the association.

The author's best thanks are due to Messrs. Albright and Wilson Ltd., Birmingham, for a grant which enabled this work to be carried out, and also to Professor E. K. Rideal, F.R.S., and Drs. A. E. Alexander and J. H. Schulman for helpful discussions.

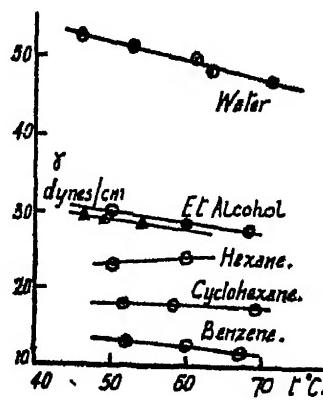


FIG. 3.

Summary.

The surface tension of molten white phosphorus has been measured.

An apparatus, which is independent of contact angle, has been devised for the measurement of interfacial tension.

Values for the interfacial tension of phosphorus against several liquids have been determined.

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THE SCHUSTER BAND OF AMMONIA, AND THE ELECTRICAL SYNTHESIS OF HYDRAZINE.

By E. J. B. WILLEY.

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In previous communications it has been shown^{1, 2} that the Schuster band at $\lambda 5635 \text{ \AA}$, developed by a glow discharge in streaming ammonia at low pressure, can be attributed to a chemiluminescent reaction :



In 1934-35 much further evidence was obtained hereupon, and the present notes are offered as guide to any who may find the topic of interest. A fuller account cannot be given since all original data, spectrograms, etc., were destroyed by enemy action before results had been worked out.

1. Intensity of Schuster Band and Yield of Hydrazine.

Fundamental to this theory was the claim by Koenig and his associates³ that a strong Schuster band must be present in the discharge spectrum if the yield of hydrazine is to be good, and in a region of pressures where preradiative deactivation of $\text{N}_2\text{H}_4'$ would be unlikely, an actual proportionality might be expected herein. The band was isolated by a monochromator from a discharge in streaming ammonia ($> 99.8\% \text{ NH}_3$) at 5 mm. pressure and its intensity measured upon a photocell. Excess NH_3 , together with any N_2H_4 , was trapped by liquid air, and permanent gases collected at the pump exhaust. So long as tube and electrodes were kept cool, the velocity of decomposition was proportional to current, as observed earlier by Davies⁴ and Westhaver,⁵ and the reaction seemed to be a volume process since its rate was independent of apparatus geometry. If heating-up was permitted, the velocity increased and a wall reaction appeared to develop as well since experimental dispositions then became important. Intensity of Schuster band was similarly proportional to current in the "cold" discharge, or until strong nitrogen bands developed and rendered its isolation doubtful. The α -bands—already attributed to chemiluminescent reaction of N_2H_4 and atomic hydrogen¹—also became noticeable at about the same point.

It would seem, therefore, that the Schuster band is associated with the primary electrical decomposition of ammonia, and the α -band with

¹ Willey, *Trans. Faraday Soc.*, 1934, 30, 230.

² Pearse and others, *Proc. Roy. Soc. A*, 1933, 143, 112; 1935, 151, 602; 1936, 155, 173; *Trans. Faraday Soc.*, 1935, 31, 786, 792.

³ Koenig and others, *Z. physik. Chem.*, A, 1928, 139, 211; 1929, 144, 213. *Bodenstein-Festband*, 1931.

⁴ Davies, *Z. physik. Chem.*, 1908, 64, 657.

⁵ Westhaver, *J. Physio. Chem.*, 1933, 37, 897.

secondary processes. In spite, however, of the utmost care in analytical arrangements, hydrazine could never be recovered, even after long runs, in quantity enough for determination. Blank experiments showed that separation of a little N_2H_4 , by boiling off large excess of NH_3 , is quite satisfactory, and one can only conclude that with the 50 cycle A.C. or D.C. glow discharges used by the writer, hydrazine did not separate in appreciable amounts. Ozoniser discharges at the same frequency through ammonia gas at atmospheric pressure also gave traces only of hydrazine, in agreement with Davis' original observations.⁴ Moreover, the exhaust gases invariably had the composition $N_2 : H_2 = 1 : 3$, which would be impossible were hydrazine leaving the discharge, since the only feasible reaction is :—



and if this were accompanied by other decomposition of NH_3 to its elements, the gaseous products would be richer in hydrogen than has been observed. This same observation as to permanent gases was made by Koenig in conditions where, however, he claimed a yield of 80 % N_2H_4 on NH_3 decomposed, two statements obviously incompatible.* Furthermore, the reaction of N_2H_4 with benzaldehyde to give benzalazine, used by Koenig to identify his product, is of little value when NH_3 is present. In this case, or with ammonia alone, a white solid is obtained which melts very nearly at the point (93° C.) given by Koenig for his material, and it is hard to avoid the conclusion that he was really dealing with impure hydrobenzamide.[†]

2. The Action of Impulse Discharges upon Ammonia.

The extremely short duration of the individual "flash" in an impulse discharge is highly favourable to reactions involving intermediate states of short duration.⁵ Since evidence is not lacking that free radicals are formed in a discharge through ammonia¹ and may be of importance in the synthesis of hydrazine, the action of such controlled impulses was studied. In rapidly-flowing NH_3 at 5-10 mm. pressure, formation of hydrazine was practically undetectable, although the amount of ammonia decomposed, calculated on a basis of molecules per coulomb, was much greater than with A.C. or D.C. discharges of the same power. The (current, reaction velocity) curve was also more quadratic in form, indicating probably a different mechanism of chemical change as compared with that obtaining in sensibly continuous discharges.

The discharge itself had moreover a vivid red colour, in marked contrast to the delicate green of other types, including those in ozonisers, and its spectrum showed most obviously very strong Balmer lines, fairly intense NH bands at $\lambda 3360$, 3370 , and some smaller emission in the further U.V. The common nitrogen bands did not appear. No trace of the Schuster band could, however, be found, even with exposures of 4 hours' duration, using a Hilger E. 3 spectrograph and Ilford hyper-sensitive panchromatic plates (H and D 7000). This observation as to loss of Schuster band in condensed discharges agrees in the main with previous studies by Rimmer⁷ who, working at higher pressures, could not, however, eliminate it entirely. It does not prove that NH can be present in excess of NH_3 and yet fail to react as suggested. A simple calculation, based upon the known frequency

* E.g. p. 222 of his first paper—*das aus Wasserstoff und Stickstoff in Volumverhältnis 1 : 3 bestehende Zersetzungsgas*. P. 217 of his second paper—*nach Verlassen des Elektrisators . . . die Analyse des Gasrestes ergab stets nahezu das theoretische Volumverhältnis $N_2 : H_2 = 1 : 3$.*

[†] Cf. Beilstein, 4th edition, Vol. 7, p. 215. For advice upon this topic the writer is indebted to Dr. J. W. H. Oldham.

⁴ Willey, *Proc. Roy. Soc., A*, 1935, 152, 158; 1937, 159, 247.

⁷ Rimmer, *Proc. Roy. Soc., A*, 1923, 103, 696.

of discharge, and the yield of permanent gases from ammonia flowing at a given rate, showed that here a very large proportion of the NH₃ actually in the path of the discharge must be decomposed at each "flash," so that NH radicals would have only a poor chance to find reaction partners during their short existence. This point is further discussed in the next section. Attention may, however, be directed to this strong development of hydrogen spectra, since it clearly suggests a means to determine reaction mechanism, and data had in fact been obtained thereupon. It may also be of interest to note that the effect persists even with very small condenser capacities and hence instantaneous power input. The NH₃ seems to be very easily decomposed—as the small amount obtained at equilibrium in the electrical synthesis would also suggest—and pass mainly to excited atomic hydrogen and NH; nitrogen, if formed in the primary reaction, appears in a non-excited condition.

3. Spectra of Various Zones of the Discharge.

A reaction NH₃ + NH → N₂H₄' → N₂H₄ + hν requires that the Schuster band shall not appear in conditions where NH cannot be formed, or NH₃ cannot exist. Existing data seem to show that this condition is satisfied.¹

As criterion for formation of NH, it would seem justifiable to adopt appearance of the λ3360, 3370 bands (3Π — 3Σ), which are clearly associated with easily-formed and low-energy states of NH since they develop in flames (*cf.* ¹ and references cited). We may therefore expect simultaneous appearance of these NH bands and the Schuster band, provided that a sufficiency of ammonia is present. The discharge tube was here made of clear quartz (22 × 1.5 cm.), and the gases entered and left through hollow electrodes of aluminium, ground into the silica, and provided with glass liners whose ends were similarly brought flat with the electrode faces; this arrangement was found necessary to prevent the discharge from running up inside the poles. A moveable shield of metal, blackened inside and fitted with a slit 1 mm. wide at right angles to the tube axis, enabled spectrograms to be taken of any desired zone of the discharge. Spectrograph and plates were as before. With D.C. at 3 mA in ammonia flowing at 10 l./hr. (measured at N.T.P.), pressure in the apparatus being 2 mm. Hg and very little decomposition taking place, the positive column showed only mild emission of Schuster and λ3360, 3370 NH bands, but cathode and anode glows gave them at high intensity, although towards visual observations they were masked by strong nitrogen bands. In no part of the discharge was it possible to obtain NH and Schuster bands independently, and in further experiments with nitrogen-hydrogen mixtures, the latter band never appeared. It is to be concluded then that in presence of excess ammonia, the emitters of (3Π → 3Σ) NH spectra, and of the Schuster band, are always coexistent, as demanded by theory.

Westhaver,¹ using a D.C. discharge in ammonia with the tube immersed in a refrigerant, obtained a condensable product only in the region of the positive column, and when the gas was less than 50 % decomposed. With the reasonable assumption that notoriously unstable N₂H₄ is undergoing decomposition by excited nitrogen obviously present in cathode and anode glows, this observation is in harmony with the above spectrographic studies and supports the theory under consideration.

4. Absorption of the Schuster Band by Hot Hydrazine Vapour.

As already pointed out, the most serious objection to a theory that the Schuster band is emitted by nascent hydrazine is the absence of a corresponding band in absorption.¹ Although this may not prove insuperable, the absorption spectrum of hot hydrazine vapour has been examined in case the transition concerned should be one from an upper state to

mildly excited vibrational levels of the ground electron state. Thermal instability of N_2H_4 , which decomposes rapidly above ca. $250^\circ C.$, will reduce the number of such levels, but might also account for the limited yield of hydrazine actually recoverable from a discharge, supposing this material to be formed in too "hot" a condition to have more than a small chance of survival.

Hydrazine was prepared from the c.p. hydrate by distillation from BaO in apparatus constructed entirely from pyrex or quartz. Part of the same apparatus was arranged as absorption tube (of quartz) so that the spectrum of a mild A.C. discharge, running as steadily as possible in a constant stream of NH_3 , could be photographed through an 85 cm. column of N_2H_4 vapour heated to $150^\circ C.$ at atmospheric pressure. Circulation of the vapour was effected by distillation between heated and cooled traps, and a single tap, protected by another trap upon which a freezing mixture was permanently maintained, served for connection to a pump for preliminary evacuation and for removal of gases formed by slight decomposition of the reagent.

Three pairs of runs were made wherein the discharge was photographed (a) with the absorption tube evacuated and (b) through a current of heated and distilling hydrazine. In two cases visual examination of the plates indicated a small but definite absorption of the Schuster band, other spectra such as the Balmer lines, the $\lambda 3360$ and 3370 NH bands, etc., having much the same intensity in both control and experimental runs. In the third case the result was not so definite.

These last experiments, together with others upon the spectroscopy of reaction products from a discharge in NH_3 , where indications were obtained as to the survival of unstable products for some seconds, the decomposition of NH_3 in various types of discharge and probable reaction mechanisms, cannot further be discussed, for reasons already given.

Summary.

Experiments are described which support the theory, already advanced, that the Schuster band of ammonia originates in a reaction:



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THE ZONE OF ACTIVATION IN RATE PROCESSES.

By R. M. BARRER.

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A recent note¹ has discussed rate processes, and compared some aspects of statistical-kinetic and transition state methods of formulation. It was claimed that wrong use was made of "squared term" statistics in dealing with flow and diffusion and that the latter were unsuited to this problem. Since the only major treatments of this kind are those of the present author,^{2, 3, 4} it was felt that the impression given in this note should be

¹ Eley, *Trans. Faraday Soc.*, 1943, 39, 168.

² Barrer, *ibid.*, 1942, 38, 322.

³ Barrer, *ibid.*, 1943, 39, 48.

⁴ Barrer, *ibid.*, 39, 59.

corrected. No wrong use of the "squared term" statistics has been made in the way suggested, and it is a purpose of this note to show how they have been used and how their proper use allows a very satisfactory formulation of rate processes. The criticism¹ is based upon the fact that it is inaccurate to replace a sequence of terms in equation (1) by the largest term in the sequence so long as E , the total energy in f degrees of freedom $\approx fRT$; and also upon the impression that in rate processes E is actually of this order. In reality, however, $E > fRT$, as is emphasised in this paper (eqns. (4) and (5)), and so long as this is true a sequence of terms may without serious error be replaced by its maximum term. It is also shown in this paper (para. 3) that the Arrhenius or apparent energy of activation would be zero when $E = fRT$, so that the criticism refers to a region seldom if ever met with in actual experiments.

The Procedure.—Experiment indicates that flow and diffusion in condensed phases require an energy of activation. The underlying idea of the zone theory is that a unit transport process may occur at a given point in the liquid when thermal energy fluctuations result in a local accumulation of adequate energy at that point; and when certain other conditions (postulate (3) below) are simultaneously fulfilled. A suitable statistics for energy fluctuations is provided in equation (1) which gives the chance (P) of finding a total energy $> E$ distributed among any number n of degrees of freedom constituting an arbitrary region :

$$P = \sum_{f=1}^n \left(\frac{E}{RT} \right)^{f-1} \frac{1}{(f-1)!} e^{-E/RT} (1)$$

In this expression the degrees of freedom involved for flow and diffusion are normally rotations (or oscillations) and inter-molecular vibrations (p. 49).² For a given E/RT , the terms in the distribution function (1) rise to a maximum as f increases to f_{\max} and then decrease (Fig. 1). The locus of the maximum is $E/RT = f$. There is a simple physical meaning of this, for at the maximum $E = fRT = \bar{U}$ where \bar{U} is the average energy in any f degrees of freedom; and as would be expected the most likely energy distribution is the average energy distribution. But equation (1) and Fig. 1 both show that on either side of the maximum there is a finite probability of finding the energy distributed among less or more degrees of freedom than corresponds to f_{\max} . Such distributions are respectively "hot" or

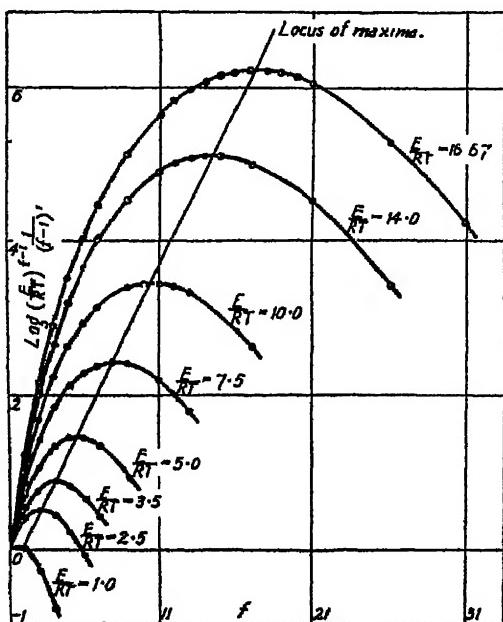


FIG. 1.

"cold," having more or less energy in them than corresponds to the average.

Now the most probable energy distribution ($E = \bar{U} = fRT$) does not define, as Eley considers,¹ the important distribution for reaction, flow or diffusion, for this would mean that these processes occurred with no apparent or Arrhenius energy of activation, E_A , at all, since then $E_A = E - \bar{U} = 0$, which is contrary to experiment. Certainly then the region in equation (1) need contain no more than $n = f_{\max}$ degrees of freedom to include all distributions likely to contribute to a successful unit process, for we may exclude all "cold" distributions.

We thus confine ourselves to "hot" distributions ($E > \bar{U} > fRT$; and $E_A > 0$). The important "hot" distributions* were then defined qualitatively by the following two postulates of the theory (p. 326):²

(1) The energy of activation for flow or diffusion should be as concentrated as possible, so that $E = E_A + \bar{U}$ is as concentrated as possible.

(2) There must be an a priori probability, defined by $(E/RT)^{f-1} \frac{1}{(f-1)!}$ of finding the important distribution, which is as large as possible bearing in mind postulate (1). Now equation (1) and Fig. 1 have already shown that the greatest a priori probability arises when $E = \bar{U}$, and so the postulates (1) and (2) together result in the actually important zones of activation being intermediate in size between $f = 1$ and $f = f_{\max}$.

To these two postulates another was added which is:

(3) There is normally need for co-operation or synchronisation between certain rotations and inter-molecular vibrations within the zone of activation before a successful unit process occurs. This introduces a factor ρ_f , where $\rho_f < 1$, multiplying each of the terms $(E/RT)^{f-1} \frac{1}{(f-1)!}$ there being a different ρ_f for each term.

It is possible as pointed out by the author (e.g. p. 63)⁴ that a spectrum of terms $\rho_f(E/RT)^{f-1} \frac{1}{(f-1)!} e^{-E/RT}$ may contribute to the probability of a successful unit process of transport, and the general formulae were developed assuming this. However, the important terms are likely to be limited in number, and in numerical applications I have replaced the summation $\sum \rho_f(E/RT)^{f-1} \frac{1}{(f-1)!}$ by its maximum term. This approximation adequately describes data where f is not very large. Viscous flow in glasses where E_A/RT is > 100 may require more terms than one.⁴

Equations of Optimum Zone Size in Viscous Flow.—It is possible to determine the most important size of "hot" zone defined by postulates (1) and (2) above. From the general viscosity functions obtained for fluids,^{3, 4} it can be shown

(i) that for apolar, polar, hydrogen and hydroxyl-bonded fluids, simple ionic melts and liquid metals

$$f = 1.45 E_A/RT \text{ for } 0 < E_A/RT < 50 \quad . \quad . \quad . \quad (2)$$

(ii) that for glasses and polymerised ionic melts

$$f = 0.44 E_A/RT \text{ for } 0 < E_A/RT < 100. \quad . \quad . \quad . \quad (3)$$

Remembering that $E_A = E - fRT$, one has from equations (2) and (3) respectively

$$\begin{aligned} f &= 0.59 E/RT & : & : & : & : & : & (4) \\ f &= 0.33 E/RT & : & : & : & : & : & (5) \end{aligned}$$

* Cf. C. N. Hinshelwood, *Kinetics of Chemical Change*, O.U.P., 1940, p. 53, for a proof that $E_A = E - \bar{U}$.

* The actual optimum "hot" zone sizes are given, as functions of E and T by equations (4) and (5).

as equations giving the most important "hot" zone size as a function of the total energy in the activated state. The loci of these equations in Fig. 1 lie well to the left of the locus of f_{\max} .

A Further Experimental Test.—When a single term in the summation $\sum p_i (E/RT)^{f-1} \frac{1}{(f-i)}$ is adequate one has for diffusion¹

$$\frac{\partial E_A}{\partial T} = -fR \quad \dots \quad \dots \quad \dots \quad \dots \quad (6)$$

and for viscous flow

$$\frac{\partial E_A}{\partial T} = -(f+1)R \quad \dots \quad \dots \quad \dots \quad \dots \quad (7)$$

where E_A is the apparent energy of activation.[†] Thus E_A has usually a negative temperature coefficient and never a positive one, according to the zone theory. On the other hand, the transition state formulation gives

$$\frac{\partial E_A}{\partial T} = R + \Delta C_v^* \quad (\Delta C_v^* = \text{the change in specific heat in passing to the transition state}) \quad \dots \quad \dots \quad \dots \quad (8)$$

which is essentially positive whenever ΔS^* , the entropy of activation, is positive.¹ Now a positive entropy is found if the zone of activation is considerable,² and so as a rule a positive $\partial E_A/\partial T$ is predicted. Abundant data are available to test this point, and for computing f by Eley's method (e.g., Barrer, Table I and Fig. 2;³ Table IV and Fig. 2).⁴ In all cases $\partial E_A/\partial T$ is negative, and in just those systems where a big zone of activation had been previously indicated, $\partial E_A/\partial T$ reaches its largest negative value. On the other hand, the transition state method requires in this case that $\partial E_A/\partial T$ reach its largest positive value. Such data emphatically favour the zone theory. A further point is that f determined from $\partial E_A/\partial T$ is usually similar to f determined from the generalised viscosity equations (3) of ref. 3 and (2) of ref. 4, by the method of p. 64.⁴

A Survey of Observed and Predicted Properties of Flow and Diffusion.—The correspondence between actual observations and predictions based upon the concept of a zone of activation in rate processes is summarised in the following table:—

Predicted Relation.

Functional relations should exist between $-\log \eta_0$ and E_A/RT or between $\log D_0$ and E_A/RT .[†]

The relation should be linear in the simplest case.

Data obtained at different temperatures should give functional relations between $-\log \eta_0$ or $\log D_0$ and E_A , the slope of which increases with decreasing temperature.

E_A should decrease with temperature at a rate proportional in the simplest case to the size of the activated zone.

Most fluids should conform in diffusion or viscous flow to generalised diffusion or viscosity equations.

Observed Relation.

Functional relations, usually linear, exist between $-\log \eta_0$ or $\log D_0$ and E_A/RT .

The slopes of curves of $-\log \eta_0$ vs. E_A increased as the temperature decreased.

E_A in all cases examined decreased as the temperature increased, at a rate usually larger the larger was η_0 or D_0 .

Apolar and polar liquids, hydroxyl and hydrogen bonded liquids, simple ionic melts, and liquid metals all conformed to a single viscosity function; and polymerised ionic melts to another characteristic function.

[†] This method must be used with discretion. It is not applicable for instance to liquid sulphur in that region where profound changes are occurring, such as the transition from rings (S_n) to chains S_m . In this region one is really dealing with a solution of S_n in S_m , the proportions of which alter rapidly with temperature.

[†] η_0 and D_0 are defined by the Arrhenius equations $\eta = \eta_0 e^{E_A/RT}$ and $D = D_0 e^{-E_A/RT}$ where η and D denote viscosity constants and diffusion constants

It should be noted that when diffusion or flow occurs by special mechanisms, such as zeolitic, Schottky, or Frenkel mechanisms in crystals,⁶ the zone theory will require modification. It has been developed for flow processes by place change only, but the degree of success achieved indicates that this mechanism predominates in simple liquids or polymers.

Summary.

The physical and statistical basis of the zone theory of diffusion and viscosity is outlined, and a criticism is shown to be unfounded. Further experimental behaviour is described which is predicted by the zone theory, but which is contrary to the transition state theory.

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⁶ Barrer, *Trans. Faraday Soc.*, 1941, 37, 590.

THE ELASTICITY OF A NETWORK OF LONG-CHAIN MOLECULES—II.

By L. R. G. TRELOAR.

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On the basis of the kinetic theory of elasticity, Wall¹ has developed a statistical method for treating the problem of the elasticity of a three-dimensional network of long-chain molecules, and has applied it to the derivation of the stress-strain relations for the simplest types of deformation of rubber-like materials, namely, elongation, unidirectional compression and shear. The significance of Wall's theoretical approach has been discussed in some detail in an earlier paper,² in which reasons were given for preferring Wall's method to the earlier attempts to solve this problem.

In the present paper the method of Wall is extended to the most general type of homogeneous deformation of rubber-like materials, of which those already considered by Wall are special cases. An expression is derived for the work of deformation, or *strain-energy* in the general case, and from this certain relations between the principal stresses and strains are obtained.

Derivation of Strain-energy Function.

In a *homogeneous* deformation the state of strain at all points of the deformed body is the same. It is defined as a displacement such that the co-ordinates of a point after the deformation are expressible as linear functions of the co-ordinates of the point before displacement. By homogeneous strain a sphere is transformed into an ellipsoid—the *strain ellipsoid*—of which the three principal axes are derived from three mutually perpendicular diameters of the sphere. In general, the directions of the

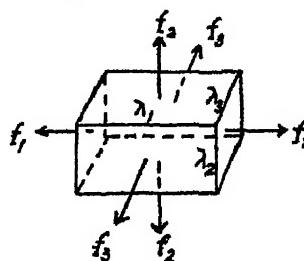


FIG. 1.—Homogeneous deformation of unit cube.

¹ Wall, *J. Chem. Physics*, 1942, 10, 485.

² Treloar, *Trans. Faraday Soc.*, 1943, 39, 36.

principal axes differ from those of the diameters of the sphere from which they were derived; in the special case where they are the same the strain is said to be *pure*. Any homogeneous strain may be resolved into a pure strain plus a rotation.* When a suitably placed cube is subjected to homogeneous strain it becomes a rectangular block (Fig. 1) having sides of length λ_1 , λ_2 , λ_3 equal to the semi-axes of the strain ellipsoid, where $\lambda_1 \geq 1$, $\lambda_2 \geq 1$ and $\lambda_3 \geq 1$ are the principal extensions. The forces f_1 , f_2 , f_3 are normal to the surfaces of the block.

In applying the molecular theory to the derivation of the strain-energy function, the following assumptions are made. (Cf. Wall.¹)

1. The N molecules of the network all have the same chain length.
2. The distribution of lengths (*i.e.* end-to-end distances) of the molecules in the undeformed state is that given by Kuhn's statistical formula.
3. On deformation, the components of length of the individual molecules are changed in the same ratio as the corresponding dimensions of the bulk rubber.
4. The deformation takes place without change of volume.

By postulate (3) a molecule whose original components of length were x , y and z will have the length-components $\lambda_1 x$, $\lambda_2 y$ and $\lambda_3 z$, after a deformation corresponding to a pure strain. Hence, if the original distribution of lengths is that given by Kuhn's formula, *i.e.*,

$$p(x, y, z) dx \cdot dy \cdot dz = \frac{\beta^3}{\pi^{3/2}} e^{-\beta^2(x^2 + y^2 + z^2)} dx \cdot dy \cdot dz \quad . \quad (1)$$

the distribution corresponding to the strained state will be

$$p'(x, y, z) dx \cdot dy \cdot dz = \frac{\beta^3}{\pi^{3/2}} e^{-\beta^2(x^2/\lambda_1^2 + y^2/\lambda_2^2 + z^2/\lambda_3^2)} dx \cdot dy \cdot dz. \quad (2)$$

Since the distribution is unaffected by a rotation the formula (2) represents equally well any homogeneous strain. If n_i is the number of molecules in the cell $\Delta x_i \cdot \Delta y_i \cdot \Delta z_i$ before deformation, and s_i the number in the same cell after deformation, the probability P of the distribution defined by (2) is related to the probability P_0 of the most probable state (1) by Wall's formula

$$\ln(P/P_0) = \sum_i s_i \ln(n_i/s_i) \quad . \quad . \quad . \quad . \quad (3)$$

where $n_i = N p(x_i, y_i, z_i) \Delta x_i \Delta y_i \Delta z_i$ and $s_i = N p'(x_i, y_i, z_i) \Delta x_i \Delta y_i \Delta z_i$.

Substitution of the appropriate values from (2) and (3) gives

$$\ln(n_i/s_i) = -\beta^2[x^2(1 - 1/\lambda_1^2) + y^2(1 - 1/\lambda_2^2) + z^2(1 - 1/\lambda_3^2)]$$

and therefore

$$\ln(P/P_0) = -\beta^2[(1 - 1/\lambda_1^2)\Sigma s_i x_i^2 + (1 - 1/\lambda_2^2)\Sigma s_i y_i^2 + (1 - 1/\lambda_3^2)\Sigma s_i z_i^2]. \quad (4)$$

Now $\Sigma s_i x_i^2 = \bar{x}^2$ where \bar{x}^2 is the mean value of x^2 for the whole assembly of molecules. By integration it may be shown that taking into account the relation (7) below, $\bar{x}^2 = \lambda_1^2/2\beta^2$. Similarly $\bar{y}^2 = \lambda_2^2/2\beta^2$ and $\bar{z}^2 = \lambda_3^2/2\beta^2$. Hence, from (4)

$$\begin{aligned} \ln(P/P_0) &= -\frac{1}{2}N[(1 - 1/\lambda_1^2)\lambda_1^2 + (1 - 1/\lambda_2^2)\lambda_2^2 + (1 - 1/\lambda_3^2)\lambda_3^2] \\ &= -\frac{1}{2}N(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3). \quad . \quad (5) \end{aligned}$$

If W is the work of deformation per c.c., *i.e.*, the strain-energy function, we may write $W = kT \ln(P/P_0)$, and therefore

$$W = \frac{1}{2}NkT(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3) \quad . \quad . \quad . \quad . \quad (6)$$

* For a fuller discussion of types of strain reference should be made to textbooks on elasticity, *e.g.*, A. E. H. Love, *Mathematical Theory of Elasticity*, Camb. Univ. Press, Chap. I.

where N now represents the number of molecules per c.c. This may be written in the alternative form

$$W = \frac{\rho RT}{2M} (\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3) \quad \dots \quad \dots \quad \dots \quad (6a)$$

where ρ is the density and M the molecular weight.

It will be seen that equation (6) reduces to the special forms given by Wall for elongation and shear (ref. ⁴, eqns. (10) and (19)) on insertion of the appropriate values of λ_1 , λ_2 , and λ_3 .

The General Stress-strain Relations:

To obtain the stress-strain relations from equation (6) it is necessary to consider a virtual displacement whereby the quantities λ_1 , λ_2 and λ_3 are increased by $d\lambda_1$, $d\lambda_2$ and $d\lambda_3$. The corresponding increase in strain energy is then calculated from (6). But the work done in the displacement may also be stated in terms of the forces f_1 , f_2 and f_3 (Fig. 1) since the work done by the force f_1 is $f_1 d\lambda_1$. From the two expressions for the virtual work thus obtained the relation between the forces (or stresses) and the principal strains may be found.

The area of the face operated on by the force f_1 is $\lambda_1 \lambda_3$, which is equal to $1/\lambda_1$, by the postulate of constancy of volume

$$\lambda_1 \lambda_2 \lambda_3 = 1. \quad \dots \quad \dots \quad \dots \quad \dots \quad \dots \quad (7)$$

The stress S_1 on this face is therefore $\lambda_1 f_1$. Similarly, $S_2 = \lambda_2 f_2$ and $S_3 = \lambda_3 f_3$. Hence the work done by the forces in a small displacement is

$$dW = \frac{S_1}{\lambda_1} d\lambda_1 + \frac{S_2}{\lambda_2} d\lambda_2 + \frac{S_3}{\lambda_3} d\lambda_3. \quad \dots \quad \dots \quad \dots \quad (8)$$

The relationship between the $d\lambda_i$ is obtained by differentiation of (7), i.e.,

$$\frac{d\lambda_2}{\lambda_3} = -\frac{d\lambda_1}{\lambda_1} - \frac{d\lambda_3}{\lambda_3}$$

which on substitution in (8) leads to the expression

$$dW = (S_1 - S_3) \frac{d\lambda_1}{\lambda_1} + (S_2 - S_3) \frac{d\lambda_3}{\lambda_3}. \quad \dots \quad \dots \quad \dots \quad (9)$$

in which λ_1 and λ_3 are independent variables which may have any values.

To obtain a second expression for dW , equation (6) is written in the form

$$W = \frac{1}{2} G (\lambda_1^2 + \lambda_2^2 + 1/\lambda_1^2 \lambda_3^2 - 3)$$

where $G = NkT$. Whence, by differentiation,

$$dW = G(\lambda_1^2 - 1/\lambda_1^2 \lambda_3^2) \frac{d\lambda_1}{\lambda_1} + G(\lambda_2^2 - 1/\lambda_1^2 \lambda_3^2) \frac{d\lambda_3}{\lambda_3}. \quad \dots \quad (10)$$

Combination of (9) and (10) leads to the stress-strain relations

$$\begin{aligned} S_1 - S_3 &= G(\lambda_1^2 - \lambda_3^2) \\ S_2 - S_3 &= G(\lambda_2^2 - \lambda_3^2) \end{aligned} \quad \dots \quad \dots \quad \dots \quad (11)$$

General Application of Stress-strain Relations.

The application of the formulae derived in the preceding paragraph to certain special problems will be considered in the next paragraph. In the present section some questions concerning the general applicability of equations (11) will be discussed. Three cases need to be distinguished, and will be considered separately.

(a) Given the Principal Strains, to find the Principal Stresses.—Insertion of the given values of λ in equations (11) leads to two simultaneous

linear equations containing the three variables S_1 , S_2 , and S_3 . It is therefore not possible to determine the stresses absolutely, but only the differences between any two. These are obtainable quite simply. This result means that if P_1 , P_2 , and P_3 are stresses satisfying equations (11), then $S_1 = P_1 + p$, $S_2 = P_2 + p$, $S_3 = P_3 + p$ will also be a solution, that is to say, the strain is not affected by the superposition of a hydrostatic pressure. This is a direct consequence of postulate (4).

(b) Given the Principal Stresses, to find the Principal Strains.—This problem is rather more difficult than the preceding one. By insertion of the given values of S_i and writing $(S_1 - S_3)/G = a$, $(S_3 - S_2)/G = b$, equations (11) become

$$\lambda_1^2 - \lambda_3^2 = a, \quad \lambda_3^2 - \lambda_2^2 = b.$$

Eliminating λ_1 and making use of the relation (7) gives

$$\lambda_3^6 + (a + b)\lambda_3^4 + ab\lambda_3^2 - 1 = 0 \quad \dots \quad (12)$$

a cubic equation in λ_3^2 which may be solved by the usual methods.

(c) Given the Applied Forces, to find the Principal Strains.—In practice it is usually not the stresses but the forces which are given. Since $S_i = \lambda_i f_i$, the stresses can only be found when the strains are already known. Equations (11) must therefore be written in terms of the forces in the directions of the principal stresses, i.e.,

$$\begin{aligned} \lambda_1 f_1 - \lambda_3 f_3 &= G(\lambda_1^2 - \lambda_3^2) \\ \lambda_3 f_3 - \lambda_2 f_2 &= G(\lambda_3^2 - \lambda_2^2). \end{aligned} \quad \dots \quad (11a)$$

There is no general solution to these equations in simple analytical terms, but a solution to a particular problem may be obtained by graphical or approximate methods. In certain cases (as illustrated in the next paragraph) the equations reduce to a form in which a simple solution may be obtained algebraically.

Applications of Equations to Particular Problems.

The following examples are included to show how the general equation (6) and the derived relations (11) and (11a) may be applied to a number of problems of practical interest involving the elastic deformation of rubber.

(a) Elongation or Unidirectional Compression.—For an elongation (or compression) of the simplest type we have $\lambda_1 = \alpha$, $\lambda_2 = \lambda_3 = \alpha^{-1}$, and $f_2 = f_3 = 0$. Therefore from the first of equations (11a),

$$f_1 = G(\alpha - 1/\alpha^2) \quad \dots \quad (13)$$

is the required relation between the applied force and the elongation ratio α . This expression was derived originally by Wall,¹ by direct application of the statistical method.

(b) Two-dimensional Extension.—For an equal extension in two dimensions (as in an inflated balloon) the state of strain is the same as in the unidirectional compression. The system of forces differs from that in (a) by the addition of a negative hydrostatic stress system. The stress normal to the extended sheet (S_1) is zero, hence, from (11) the stress in the sheet is

$$S_3 = S_2 = G(1/\alpha - \alpha^2)$$

where α is the ratio of the final to the original thickness. It is convenient to consider the force across a section of the sheet 1 cm. in length (analogous to surface tension). If this is denoted by t , then

$$t = S_3 \alpha = G(1/\alpha - \alpha^2). \quad \dots \quad (14)$$

This shows that for moderately large extensions (e.g., $\alpha < 1/3$) the tension in the sheet is independent of the extension.

(c) Shear.—Consider a sheet of rubber stretched in the direction OX by forces f_1 , and let forces f_2 be applied in the direction OY of such magnitude that the dimension of the sheet in this direction remains unchanged (Fig. 2). In this case if we put $\lambda_1 = \alpha$, we have $\lambda_2 = 1$ and $\lambda_3 = 1/\alpha$, so that the state of strain is a shear. It is required to find the relation between the two principal stresses in the sheet and α , and also the relation between shear stress and shear strain.

Since the stress normal to the sheet is zero, $S_3 = 0$, and hence, from equations (11)

$$\begin{aligned} S_1 &= G(\alpha^2 - 1/\alpha^2) & f_1 &= G(\alpha - 1/\alpha^2) \\ S_2 &= G(1 - 1/\alpha^2) & f_2 &= G(1 - 1/\alpha^2) \end{aligned} \quad . . . \quad (15)$$

It will be observed that the ratio of f_1 to f_2 is not constant, and that f_2 tends towards a constant value for large values of α . For small strains, i.e. $\alpha \sim 1$, $df_1/d\alpha = 4G$, whilst $df_2/d\alpha = 2G$, and therefore $f_1 = 2f_2$. For a simple elongation the initial value of $df_1/d\alpha$ is $3G$. Hence, comparing the tension in a simple elongation with the tension in the direction of α in what may be called a "shear elongation," it is seen that for small deformations the latter is greater than the former in the ratio $4/3$, whilst for large deformations the two become equal.

To obtain the relation between shear stress and shear strain use is made of the strain-energy function (6). This gives

$$W = \frac{1}{2}G(\alpha^2 + 1/\alpha^2 - 2) = \frac{1}{2}G\sigma^2 \quad . . . \quad (16)$$

where $\sigma (= \alpha - 1/\alpha)$ is the amount of the shear. As pointed out by Wall¹ this is equivalent to a linear relation between shear stress F_σ and shear strain of the form $F_\sigma = G\sigma$.

(d) Elongation Plus Shear in Plane at Right Angles to Elongation.—A problem of particular interest concerns the energy required to shear a body in the plane (y, z) after it has been given an initial elongation (or compression) in the direction OX. For the initial elongation the strained dimensions of the unit cube are given by $\lambda_1 = \alpha$, $\lambda_2 = \lambda_3 = \alpha^{-\frac{1}{2}}$. With the superposition of a shear these become $\lambda_1 = \alpha$, $\lambda_2 = \alpha^{-\frac{1}{2}}\beta$, $\lambda_3 = \alpha^{-\frac{1}{2}}/\beta$, the amount of the shear being $\sigma = \beta - 1/\beta$. From (7) the total work is

$$W = \frac{1}{2}G(\alpha^2 + \beta^2/\alpha + 1/\alpha\beta^2 - 3).$$

The work due to the original elongation is

$$W_\alpha = \frac{1}{2}G(\alpha^2 + 2/\alpha - 3).$$

The difference is the work due to the shear, i.e.,

$$W_\sigma = \frac{1}{2}G(\beta^2 - 2 + 1/\beta^2)/\alpha = \frac{1}{2}G\sigma^2/\alpha. \quad . . . \quad (17)$$

This gives the interesting result that Hooke's Law is obeyed in shear in any plane at right angles to a simple elongation (or compression) but with an effective modulus of rigidity *inversely proportional to the original elongation*.

Comparison with Mooney's Theory.

The equations derived from the molecular theory, and in particular equation (6), resemble very closely the formulæ derived by Mooney.²

¹ Mooney, *J. Appl. Physics*, 1940, 11, 582.

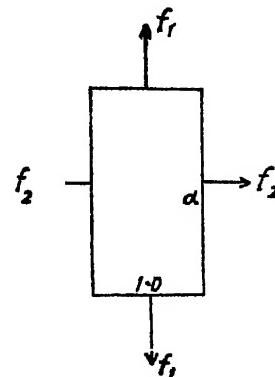


FIG. 2.—Rubber sheet in shear.

Mooney's argument is of a very general mathematical character, and takes no account of physical structure. His basic assumptions are (1) that the material is isotropic, and after an elongation (or compression) it remains isotropic in a plane at right angles to the elongation, (2) that the traction (*i.e.* shear stress) in simple shear in any isotropic plane is proportional to the shear (Hooke's Law), and (3) that there is no volume change on deformation. Mooney's expression for the strain energy is

$$W = \frac{G}{4} \sum_{i=1}^3 (\lambda_i - 1/\lambda_i)^2 + \frac{H}{4} \sum_{i=1}^3 (\lambda_i^3 - 1/\lambda_i^3). (18)$$

Equation (6), derived from the molecular theory, is a special case of (18), and is obtained therefrom by writing $G = H = NkT$. Again, the result represented by equation (17) is a special case of Mooney's second assumption. But whereas Mooney's theory leaves two constants, G and H , to be determined by the specific properties of the material, the molecular theory involves only one independent constant characteristic of the material for the description of the general elastic behaviour of a rubber.

Limitation of Theory.

It must be emphasised that the molecular network theory is limited in its practical application to rubber by the inadequacy of certain of its fundamental assumptions. The most serious discrepancy is likely to arise in connection with the assumption of Kuhn's distribution formula (7), which applies only so long as no important fraction of the molecules have lengths approaching the length of the fully extended chain. This will mean that the formula (6) will cease to be applicable when any one of the λ is large (*e.g.*, greater than about 5 in the case of a normal vulcanised natural rubber). To obtain the stress-strain relations for larger deformations it would be necessary to make use of a more accurate expression than (1) for the distribution of molecular lengths. A beginning has been made by the derivation of a distribution function for paraffin molecules which is reasonably accurate over the whole range of molecular lengths.⁴

Summary.

Wall's treatment of the elasticity of a molecular network is extended to cover the general homogeneous type of deformation of rubber. An equation is derived for the work of deformation in terms of the three principal strains, from which certain general stress-strain relations are deduced. These relations involve only one physical constant of the material. The use of the formulae is illustrated by their application to a number of simple cases. It is shown that the effective rigidity in respect of a shear in a plane at right angles to a previous elongation is inversely proportional to the elongation.

This work forms part of the programme of fundamental research on rubber undertaken by the Board of the British Rubber Producers' Research Association.

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⁴ Treloar, *Proc. Physic. Soc., in press.*

THE ELECTRICAL CONDUCTIVITY OF COLLOIDS.

By T. R. BOLAM AND A. K. M. TRIVEDI.

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One of the most striking features of the behaviour of solutions of soaps and similar paraffin-chain electrolytes is that at relatively high concentrations the equivalent conductivity in many cases *increases* with increase in the concentration. While it is generally agreed that the anomaly is connected with the presence of ionic micelles, *i.e.* colloidal units formed by aggregation of the fatty ions, opinions differ concerning the precise origin of the effect. In a theory advanced by Hartley,¹ the micelles are regarded as highly polyvalent ions, and the increase in conductivity is ascribed to the smoothing out of the variations, due to strong interionic action, in the distribution of the oppositely charged ions. As Hartley points out, the theory should apply to ordinary electrolytes of extremely unsymmetrical valence-type, but it should also apply to inorganic colloids in which the particles are charged by the adsorption of ions. The object of the present investigation was to ascertain if colloidal systems of this kind do actually show an anomalous increase in conductivity.

The measurements were made on sulphur sols prepared by the method of Odén, *i.e.* colloidal sulphur produced by the interaction of $\text{Na}_2\text{S}_2\text{O}_8$ and H_2SO_4 , was alternately coagulated by NaCl and redispersed in water until acid was completely eliminated. In such sols the colloidal units or micelles are sulphur particles carrying adsorbed polythionate ions produced by chemical action accompanying the formation of the colloidal sulphur. The only other chemical species present are sodium and chloride ions. At first all the polythionate ions are adsorbed or bound (probably as hexathionate) by the sulphur, but eventually a certain proportion become free (as pentathionate) and pass, along with an equivalent amount of sodium ions, into the intermicellar liquid, where the sodium chloride is situated. On dilution of the sol, further liberation of bound polythionate tends to occur, but it is found that the amount of change taking place during the period of measurement is negligible, provided the dilution is kept within certain limits. These sulphur sols are particularly suitable for the purpose in view. They can be obtained in high concentrations, and their constitution quantitatively determined by chemical analysis.² In contrast with solutions of colloidal electrolytes, there is no question of the existence of two distinct types of micelle, or of appreciable variation, on dilution, in the relative proportions of the colloidal and crystalloidal constituents.

Experimental.

The Effect of Dilution on the Conductivity of Sulphur Sol.—The measurements were made on two sols (I and II) prepared and analysed by methods previously described.³ A high concentration of bound polythionate and a relatively low concentration of NaCl were secured by coagulating the sulphur at about 5° C. with 0.2 N. salt, and reprecipitating the coagulum in a suitable volume of water. In order that the distribution of polythionate between micelles and intermicellar liquid should

¹ Hartley, *Kolloid-Z.*, 1939, 88, 22.

² Bolam and Trivedi, *Trans. Faraday Soc.*, 1942, 38, 140.

reach a sufficiently steady state, the sols were kept for some days at 25° C. before use. The sols were quite transparent at room temperature. Table I

TABLE I.—COMPOSITION OF SOLS.

Sol.	Sulphur (g./l.).	Polythionate (m.e./l.).		gives the composition of each sol, as determined immediately after the respective conductivity measurements. With one exception (indicated by brackets) the polythionate was estimated as barium sulphate, this being considered more reliable than estimation as silver
		Bound.	Frie.	
II	212.0	55.04	260.8	(32.52)
	212.0	55.04	261.1	31.75
	Mean 212.0	55.04	261.0	31.75
	296.9	55.04	385.2	28.63
	299.2	54.64	389.5	29.22
	Mean 298.1	54.84	387.4	28.93

sulphide. Concentrations are expressed as grams or milli-equivalents of material in one litre of *sol*.

Conductivities were measured at 25 ± 0.03 ° C. by a method described elsewhere.³ Two cells were employed, one (I) having fixed vertical electrodes (constant = 0.1829), and the other (II), removable horizontal electrodes (constant = 0.5669). Water of specific conductivity 1.1×10^{-6} was used throughout. Taking the relative concentration of the original sol as unity, relative concentrations of 0.5, 0.25 and 0.1 were obtained by dilution, as follows: 50 ml. sol + 50 ml. water; 25 ml. sol + 75 ml. water; 10 ml. sol + 90 ml. water. The dilutions were performed together immediately before the conductivity measurements, and the resulting sols were kept at about 5° C. until required, in order to minimise the formation of free polythionate. In the case of sol I the liquid was at room temperature when placed in the cell, but in the case of sol II the liquid was kept at 25° C. for about half an hour before being placed in the cell. The experimental data are shown in Table II, where *c* is the relative concentration, *t* is the time interval (minutes) between placing the cell in the thermostat (immediately after filling) and measuring the conductivity, and *R* is the observed resistance (ohms).

It should be mentioned that the electrodes adsorbed sulphur in some form or other, since on replacing colloidal sulphur in the cell by water (after thorough washing of cell and electrodes with water), the conductivity of the latter was found to increase considerably, and addition of BaCl₂ showed that sulphate was being produced to a corresponding extent (AgNO₃ gave no precipitate, indicating the absence of polythionate). The only data which are at all likely to be in error as the result of this action of the electrodes are those for *c* = 0.1, where the observed resistance decreased appreciably with time. However, liberation of a very small quantity of polythionate from the micelles would have the same effect (see below), and experience has shown that the rate of liberation increases with increase in the extent of dilution.

The Influence of Ageing on the Conductivity of Sulphur Sols.—The conductivities of two sols (III and IV) were measured (a) shortly after preparation, and (b) after standing for some weeks at room temperature. The results (obtained with cell I) are given in Table III, where κ_{sol} is the specific conductivity (mho) of the sol.

The Influence of Colloidal Sulphur on the Distribution of Electrolytes in Membrane Equilibria.—In these experiments a collodion bag containing 50 to 60 ml. of sulphur sol was suspended in water until mem-

³ Bolam and Hope, J.C.S., 1941, 843.

brane equilibrium was established (for experimental details, see ref. 2). The inside (1) and outside (2) liquids were then analysed for sulphur, etc. Most of the experiments were performed at room temperature (16° - 18° C.).

TABLE II.—VARIATION OF CONDUCTIVITY WITH DILUTION.

Sol. I.				Sol. II.			
c.	t.	R.	Re.	c.	t.	R.	Re.
1·0	30	14·26	14·25	1·0	11	11·87	
	—	14·24			16	11·89	
	—	14·24			23	11·88	
	125	14·25			31	11·88	
	Mean	14·25			Mean	11·88	11·88
	—	—			(Cell II)	—	
0·5	30	29·60	14·80	0·5	5	36·60	
	42	29·60			15	36·60	
	49	29·60			24	36·60	
	52	29·60			—	36·60	
	61	29·60			Mean	36·60	*11·81
	—	Mean	29·60		—	—	
0·25	22	60·9	15·22	0·25	13	25·20	
	24	61·1			18	25·15	
	—	60·9			27	25·15	
	37	60·8			30	25·15	
	—	Mean	60·9		Mean	25·16	12·58
	—	—	—		—	—	
0·1	22	152·0	15·20	0·1	18	53·6	
	—	151·9			25	53·4	
	38	150·8			30	53·4	
	44	149·6			—	—	
	—	—			Mean	53·5	13·38
	—	—			—	—	
·	—	—	(Cell II)	0·1	13	136·8	13·68
	—	—			25	135·8	
	—	—			35	135·0	
	—	—			43	134·6	
	—	—			21	425	
	—	—			28	424	
	—	—			46	422	
	—	—			56	421	
	—	—			—	—	
	—	—			—	—	*13·71

* 0·1829 Re/0·5669.

TABLE III.—CONDUCTIVITY BEFORE AND AFTER AGEING.

Sol.	Sulphur (g./l.).	Chloride (m.e./l.).	Polythionate (m.e./l.).			R.	$\kappa_{sol} \times 10^4$.
			Bound.	Free.	Total.		
III (a)	53·2	6·78	58·09	2·31	60·40	136·3	1·342
	46·9	6·98	51·12	9·30	60·42	86·8	2·107
IV (a)	101·1	18·34	133·6	(4·2)*	137·8	48·7	3·756
	93·1	18·55	118·0	19·36	137·4	33·3	5·493

* Estimated as silver sulphide.

but in a few instances the apparatus was kept in ice, or in an air-thermostat maintained at 25° C. Any influence due to variation in temperature was found to be negligible under the given conditions. Representative data

are given in Table IV, where $[S]$ is the concentration (g./l.) of sulphur, and $[Cl]$, $[P_b]$, and $[P_f]$ are the concentrations (m.e./l.) of chloride, bound

TABLE IV.—DISTRIBUTION OF ELECTROLYTES IN MEMBRANE EQUILIBRIA.

Expt.	$[S]_1$	$[S]_2$	$[Cl]_1$	$[Cl]_2$	$[P_b]_1$	$[P_b]_2$	$[P_f]_1$	$[P_f]_2$
1	102.5	12.04	24.59	29.32	81.53	14.36	9.64	13.03
2	77.66	18.87	26.33	29.95	82.56	20.66	10.45	12.85
3	35.33	3.76	35.60	37.84	38.26	7.43	3.00	3.30
4	26.28	12.17	8.29	8.99	30.99	14.85	4.16	4.76

and free polythionate respectively. Bound polythionate was estimated as silver sulphide, and free polythionate as barium sulphate.

Discussion.

The data in Table II reveal that when a sulphur sol is diluted, the value of the product Rc increases; that is to say the specific conductivity decreases more rapidly than would be the case if it varied in direct proportion to the concentration. It is to be expected that a simple mixture of sodium polythionate and sodium chloride would behave in the reverse fashion, as happens, for example, with a mixture of sodium sulphate and sodium chloride.⁴ Thus it appears that sulphur sols show a distinctive behaviour, due to the circumstance that a proportion of the polythionate ions are adsorbed by the colloidal particles of sulphur; for it is difficult to see how the mere presence of the particles, as such, could have any appreciable effect, one way or the other, on the conductivity.

It will be seen from Table III that as the sol ages the specific conductivity increases to an extent directly proportional to the increase in free polythionate; actually 0.109 and 0.108×10^{-8} mho per milliequivalent for sol III and sol IV respectively. This shows that the increase in conductivity on ageing is due to the liberation of polythionate from the micelles, and that the equivalent conductivity of the free polythionate (Λ_{NaP_f}) is roughly 109. Direct measurements of the equivalent conductivity of sodium pentathionate in pure aqueous solutions (Λ_{NaP}) are lacking, but approximate values may be derived from the data of Hertlein⁵ for potassium pentathionate by means of the expression

$$\Lambda_{NaP} = \Lambda_{K_P} - (\Lambda_{K_2SO_4} - \Lambda_{Na_2SO_4}).$$

Employing the data for sodium and potassium sulphates given in the International Critical Tables,⁶ it is found that Λ_{NaP} varies from about 96 to about 110 over the range of concentrations covered by the free polythionate in sols III and IV. Since Λ_{NaP_f} is substantially the same as Λ_{NaP} , it follows that the micelles do not exert any appreciable repressive influence on the conductivities of the electrolytes located in the intermicellar liquid.

In Table V are recorded values for the equivalent conductivity of the bound polythionate (Λ_{NaP_b}), as calculated by the formula

$$\Lambda_{NaP_b} (\text{m.e. of } NaP_b \text{ per l.}) = \kappa_{\text{sol}} - \kappa_{NaCl} - \Lambda_{NaP_f} (\text{m.e. of } NaP_f \text{ per l.}),$$

where the conductivities of sodium chloride and free polythionate are assumed to be the same as in pure aqueous solutions of the salts at the same concentrations as in the sol. The values of Λ_{NaP_f} were derived

⁴ Smith and Gortner, *J. Physical Chem.*, 1933, 37, 78.

⁵ Hertlein, *Z. physikal. Chem.*, 1896, 19, 269.

as described above, and those of κ_{NaCl} were obtained partly by direct measurement and partly, by interpolation, from the appropriate data in the International Critical Tables.⁴ The calculation appears to be justified by the fact that the behaviour of sodium chloride and sodium sulphate in mixed solutions is additive over the range of concentrations under consideration.⁴ As Table V shows, A_{NaP_b} is always very much less than

TABLE V.—EQUIVALENT CONDUCTIVITIES OF BOUND AND FREE POLYTHIONATE.

Sol.	<i>c.</i>	Concn. NaP _b (m.e./l.).	$\kappa_{\text{sol}} \cdot 10^3$.	$\kappa_{\text{NaCl}} \cdot 10^3$.	A_{NaP_f} .	A_{NaP_b} .
I	1.0	261.0	12.84	6.077	91.9	14.7
	0.5	130.5	6.179	3.145	97.8	11.4
	0.25	65.3	3.003	1.616	102.9	8.7
	0.1	26.1	1.203*	0.6631	108.7	7.5
II	1.0	387.4	15.39†	6.054	92.8	17.2
	0.5	193.7	7.271	3.134	98.4	14.0
	0.25	96.9	3.418	1.611	103.8	10.9
	0.1	38.74	1.338*†	0.6607	109.0	9.4
III (a)	—	58.1	1.342	0.8137	110.2	4.7
	(b)	51.1	2.107	0.8377	101.9	6.3
IV (a)	—	133.6	3.756	2.131	107.0	8.8
	(b)	118.0	5.493	2.156	96.2	12.5

* Initial reading.

† Cell I.

A_{NaP_f} . The differences are too large to be due solely to decrease in the conductivity of the polythionate ions as the result of adsorption on the sulphur particles, and it must be concluded that the conductivity of the compensating sodium ions is markedly reduced by the electrostatic attraction of the charged particles.

The results obtained from membrane equilibria are consistent with this conclusion, as the following considerations show. It is seen from Table IV that the amount of chloride (or free polythionate) in unit volume of sol is always less in the more concentrated sol (1) than in the other (2). Part, at least, of the inequality in distribution is due to the difference in the proportion of the volume of the sol occupied by the sulphur particles and their associated non-solvent water. For example, if $[\text{Cl}]'$ is the true concentration of chloride (m.e./l. with respect to solvent water), then $[\text{Cl}]' = 1000 [\text{Cl}]/(1000 - [\text{S}]/D)$, where D is the apparent density of the hydrated sulphur. The values of $[\text{Cl}]'$, etc., obtained by taking $D = 1.0$ (see Table I of ref. 2) are given in Table VI. In all cases $[\text{Cl}]'_1$ is greater than $[\text{Cl}]'_2$ by an amount far in excess of the probable experimental error. This indicates that the equilibrium is of the Donnan type, due to the inequality in the distribution of the bound polythionate. The distribution of the free polythionate (bivalent anion) is also in harmony with this view. As Table VI shows, the ratio $[\text{P}_t]'_1/[\text{P}_t]'_2$ is definitely closer to $([\text{Cl}]'_1)^2/([\text{Cl}]'_2)^2$ than to $[\text{Cl}]'_1/[\text{Cl}]'_2$.

Assuming that the activities of the chloride and sodium ions are identical with their (relatively low) concentrations, we have

$$\gamma = \frac{[\text{Cl}]'_1}{[\text{Cl}]'_2} = \frac{[\text{Na}]'_1}{[\text{Na}]'_2} = \frac{[\text{Cl}]'_1 + [\text{P}_t]'_1 + [\text{Na}_m]'_1}{[\text{Cl}]'_2 + [\text{P}_t]'_2 + [\text{Na}_m]'_2}$$

where $[\text{Na}_m]'$ is the apparent concentration (activity) of the compensating sodium ions. Since the actual concentration of compensating ions (with

* I.C.T., IV, pp. 233, 236, 237.

respect to solvent water) is $[P_b]'$, we have $[Na_m]' = \alpha[P_b]'$. Hence, assuming that α has the same value in (1) and (2), we have

$$\frac{r([Cl]_1' + [P_t]_1') - ([Cl]_1' + [P_t]_1')}{[P_b]_1' - r[P_b]_1'}.$$

TABLE VI.—ACTIVITY OF COMPENSATING IONS.

Expt.	$[Cl]_1'$	$[Cl]_2'$	$[P_t]_1'$	$[P_t]_2'$	$\frac{[Cl]_2'}{[Cl]_1'}$	$\frac{([Cl]_2')^2}{([Cl]_1')^2}$	$\frac{[P_t]_2'}{[P_t]_1'}$	$[P_b]_1'$	$[P_b]_2'$	$\alpha_{tot.}$
1	27.40	29.68	10.74	13.18	1.08	1.17	1.23	90.86	14.53	10.8
2	28.56	30.53	11.33	13.10	1.07	1.15	1.16	89.54	21.06	10.2
3	36.90	37.98	3.11	3.31	1.03	1.06	1.06	39.67	7.46	7.8
4	8.52	9.10	4.27	4.82	1.07	1.15	1.13	31.84	15.04	6.8

The low values of α obtained (Table VI) are similar to those derived, in essentially the same way, for other inorganic colloids, e.g., chromic oxide⁷ and stannic oxide.⁸ Since α is comparable with the ratio of A_{NaP_b} to A_s for sodium pentathionate (ca. 120), the membrane equilibria data provide further support for the view that there is strong interionic action between the adsorbed polythionate ions and their compensating sodium ions. It seems probable that ionic association (ion-pair formation) occurs to a marked degree. McBain and Thomas⁹ have found that 89.5 per cent. of the compensating chloride ions in ferric oxide sols travel to the cathode, and hence must be carried along by the positive colloidal particles.

On plotting A_{NaP_b} against the concentration of bound polythionate, separate curves are obtained for sols I and II. If, however, the values

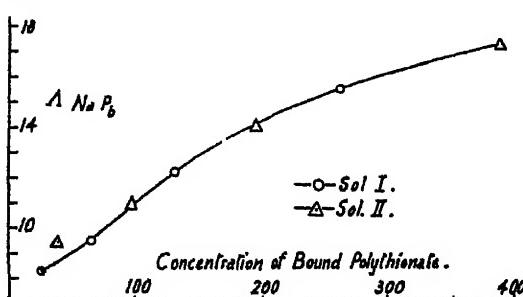
of A_{NaP_b} for sol I are uniformly increased by 0.8, the points (with one exception) lie on common curve (see figure). It is evident that the two sols behave essentially in the same way and that A_{NaP_b} increases with increase in the concentration of the sol. This result, considered along with the fact that the adsorption of poly-

thionate ions by the sulphur particles, a process equivalent in some degree to aggregation of these ions, is accompanied by a marked decrease in the conductivity of the sodium polythionate concerned, appears to provide qualitative support for Hartley's theory. Further data are required to decide if the theory does actually account for the anomalous behaviour of sulphur sols. In particular it is necessary to ascertain how the conductivity varies when the concentration of bound polythionate is changed, while the concentrations of chloride and free polythionate are kept constant.

⁷ Bjerrum, *Z. physikal. Chem.*, 1924, 110, 656. Rinde, *Phil. Mag.* (7), 1926, I, 32.

⁸ Ghosh, *J.C.S.*, 1929, 2290.

⁹ McBain and Thomas, *J. Physical Chem.*, 1936, 40, 997.



Summary.

i. The electrical conductivity of Odén sulphur sols is anomalous in that on dilution the specific conductivity decreases more rapidly than does the concentration of the sol.

2. Conductivity measurements and membrane equilibrium data indicate that while the free polythionate in sulphur sols shows normal behaviour, strong interionic action occurs between the bound polythionate ions and their compensating oppositely-charged ions.

3. The equivalent conductivity of the bound polythionate appears to increase with increase in the sol concentration, in qualitative agreement with Hartley's theory of the conductivity of solutions containing electrolytes of extremely unsymmetrical valence-type.

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RATES AND EQUILIBRIA IN THE IONISATION OF C-H BONDS.

By R. P. BELL.

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Although the C—H bonds of the paraffin hydrocarbons show no observable tendency to split off a proton in aqueous solution, this tendency becomes apparent when the molecule contains active groups such as the carbonyl or nitro groups.^{1, 2} If such a compound SH is in solution in the presence of a basic anion B⁻ (e.g. the hydroxyl ion, or the anion of any weak acid) the equilibrium



will be set up. We can then define an equilibrium constant

$$K = \frac{[BH][S^-]}{[SH][B^-]} = \frac{K_{\text{sh}}}{K_{\text{bh}}} \quad . \quad . \quad . \quad . \quad . \quad (i)$$

where K_{SH} and K_{BH} are the acid strengths of the species SH and BH as usually defined. The velocity of the reaction from left to right can be represented by a bimolecular velocity constant k .

By varying the chemical nature of SH and BH the values of both K_{SH} and k can be varied over a wide range. If these variations are confined to a series of similar compounds, it is reasonable to suppose that for a given temperature and solvent the velocity constant k will be a unique function of the values of K_{SH} and K_{BH} . For any small change in the nature of SH and BH we can therefore write

$$\delta \log k = \beta \delta \log K_{\text{BH}} - \alpha \delta \log K_{\text{BH}} \quad . \quad . \quad . \quad (2)$$

where α and β are positive quantities which may themselves be functions of K_{AH} and K_{BH} , but which can be taken as constants for not too large ranges of velocity or acid strength. Relationships like equation (2) have been interpreted in terms of a molecular picture of proton-transfer reactions.^{3, 4, 5}. In terms of this picture equation (2) implies that the re-

² Wilson, *Trans. Faraday Soc.*, 1938, 34, 175.

² Bonhoeffer, Geib and Reitz, *J. Chem. Physics*, 1939, 7, 664.

³ Horiuti and Polanyi, *Acta Phys. U.R.S.S.*, 1935, 2, 505.

⁴ Bell, *Proc. Roy. Soc. A*, 1936, 154, 414.

⁵ Bell and Lidwell, *ibid.*, 1940, 176, 114.

pulsive forces between the reactants are the same for all members of the series, and that the shapes and positions of the potential energy curves involved are determined completely by the values of K_{SH} and K_{BH} . If we make the further assumption that a change within the series has no effect on the shapes of the curves, but only shifts their position relative to one another along the energy axis, then the potential energy diagram predicts that $\alpha = \beta < 1$, so that equation (2) becomes

$$\delta \log k - \alpha(\delta \log K_{SH} - \delta \log K_{BH}) = \alpha \delta \log K \quad . . . \quad (3)$$

k is now a function only of K (rather than of K_{SH} and K_{BH} separately), and it may be anticipated that α will be effectively constant over a range of at least a few powers of ten of k or K .

The Ionisation of Ketones.

Ionisation velocities low enough to be measured are normally found only in pseudo-acids, *i.e.* compounds where the structure of the anion S^- differs from that of SH . For example, compounds containing the groups

$CH \cdot CO^-$ or $\begin{array}{c} > \\ CH \cdot NO_2 \end{array}$, give respectively the ions $\begin{array}{c} > \\ C : C - O \end{array}$ and

$C : N \begin{array}{c} + \\ \diagdown \\ \ddot{O} \\ \diagup \\ \ddot{O} \end{array}$. In a few cases the reaction velocity of SH with a base B^-

can be directly measured, as in the slow neutralisation of the nitro-paraffins by hydroxyl ions. More frequently, however, indirect methods have to be used, and rates of halogenation, deuterium exchange or racemisation have been used to measure the rate of ionisation of the group $\begin{array}{c} > \\ CH \cdot CO^-$ (*cf.* Wilson¹). In these cases the base B^- is not used up, and plays the part of a catalyst. The catalytic constants as usually defined are then equivalent to the bimolecular velocity constants for the reaction between ketone and base.

For a given ketone equation (2) or (3) is equivalent to the well-known Brönsted relation between catalytic power and basic strength. By using as catalysts the anions of carboxylic acids this relation has been shown to hold for the halogenation of a number of ketones and related substances,^{*} the value of the exponent α varying from one ketone to another. On the other hand, the acid strengths of the ketones used are not sufficiently accessible to detect any relationship between k and K_{SH} , though it seems likely that such a relationship exists, since the experimental values of $\alpha (= - d \log k / d \log K_{BH})$ decreased steadily with increasing rate of ionisation. In the present paper we shall show that it is possible on the basis of reasonable assumptions to deduce approximate values of K_{SH} from the kinetic results, and to compare them with other experimental data.

The experimental results are summarised in Table I. R is the velocity constant for the reaction between the ketone and a hypothetical anion having $K_{BH} = 10^{-4}$, corrected for statistical differences between the different ketones; R_{OH} is the corresponding constant for reaction with hydroxyl ions; α is the value of the exponent derived from measurements with anions having $K_{BH} = 10^{-6} - 10^{-5}$. The data for substances (1), (4), (5), (6), (7), (9), (10) and (12) are taken from the work of Bell and Lidwell² on the rates of halogenation, where the methods of calculating R , R_{OH} and α are described.^{*} The data for malonic ester (8) are from similar measurements in this laboratory by Dr. D. H. Everett, while those for

^{*} Bell and Lidwell, *ibid.*, 88.

^{**} The value of R_{OH} for monochloracetone in the original reference is in error by a power of 10; it has been corrected here.

TABLE I

Ketone.	$\log_{10} R$.	$\log_{10} R_{OH^-}$	α .	$-\log_{10} K_{BH^+}$	α_{OH^-}
(1) $\text{C}_2\text{H}_5\text{COCH}_3$	—	—	0.88	20.0	0.54
(2) CH_3CHO	—	(—6.05)	—	19.7	—
(3) $\text{CH}_3\text{COCH}_2\text{H}_5$	—5.60	—	—	19.2	—
(4) $\text{C}_2\text{H}_5\text{COCH}_2\text{C}_2\text{H}_5\text{COCH}_3$	—5.16	1.40	0.89	18.7	0.56
(5) $\text{CH}_3\text{COCH}_2\text{Cl}$	—3.21	3.45	0.82	16.5	0.29
(6) $\text{CH}_3\text{COCH}_2\text{Br}$	—2.95	3.78	0.82	16.1	0.29
(7) $\text{CH}_3\text{COCHCl}_2$	—2.00	4.73	0.82	14.9	0.29
(8) $\text{CH}_3(\text{COOC}_2\text{H}_5)_2$	—0.47	5.88	0.80	12.9	0.27
(9) $\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$	+1.02	—	0.59	10.7	—
(10) $\text{CH}_3\text{COCH}_2\text{COCH}_3$	+1.83	—	0.52	9.3	—
(11) $\text{CH}_3\text{COCH}_2\text{BrCOOC}_2\text{H}_5$	+2.22	—	0.64	8.5	—
(12) $\text{CH}_3\text{COCH}_2\text{COOH}$	+2.57	—	0.48	7.8	—

α -bromacetone are given by Pedersen.⁷ The value of R for acetophenone (3) is estimated from measurements on its rate of iodination in trimethylacetate buffers: on account of the low solubility of this ketone a complete study was not attempted. Finally, the value of R_{OH^-} for acetaldehyde (2) is obtained from the measurements of Bell⁸ on the rate at which it condenses to aldol in presence of hydroxyl ions. This reaction is of the first order with respect to acetaldehyde, and almost certainly depends on the rate of ionisation of the aldehyde.⁹ The value of R for acetaldehyde has not been measured, and the value in the table was obtained by multiplying the value for acetone by 1.8, which is the ratio between the R_{OH^-} values for the two substances.

Table I shows clearly that α decreases as R increases, and it was previously suggested⁴ that $\alpha/(1 - \alpha)$ (representing the ratio of the slopes of the two potential energy curves at the point of crossing) was roughly a linear function of $\log_{10} R$. However, if this relationship is extrapolated to $\alpha = 0$ it predicts a maximum value for R of about 10^8 , which is unlikely, since in our present units the collision number is about 10^{11} . We have therefore preferred to assume a linear relation between $\log_{10} R$ and $\cot \pi \alpha$, which allows $\log_{10} R$ to become infinite for $\alpha = 0$ and $\alpha = 1$. Of course no theoretical significance is claimed for this form of relationship, but it is a convenient one for interpolations or short extrapolations. Fig. 1 (circles) shows a plot of $\log_{10} R$ against $\cot \pi \alpha$, the straight line representing

$$\log_{10} R = 2.16 + 2.92 \cot \pi \alpha \quad . \quad . \quad . \quad (4)$$

The numbers of the points correspond to the numbering of the ketones in Table I. Some of the deviations are undoubtedly greater than the experimental error, but the general trend is satisfactorily represented.

⁷ Pedersen, *J. Physic. Chem.*, 1933, **37**, 751; 1934, **38**, 99, 601.

⁸ Bell, *J. Chem. Soc.*, 1937, 1637.

⁹ Watson, *Trans. Faraday Soc.*, 1941, **37**, 707.

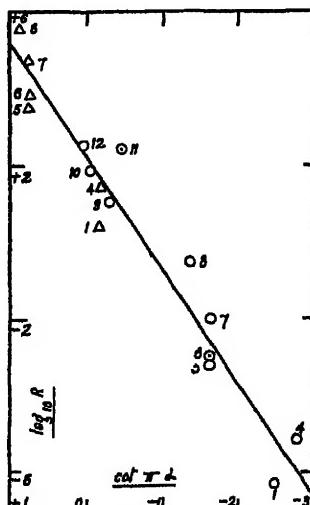


FIG. 1.

If we now assume that the exponent α is the same for variations of ketone as it is for variations of catalyst (*i.e.*, that equation (3) is valid), we can calculate approximate values for the dissociation constants of the ketones used. Since the values of R all refer to a constant catalyst, the relation between K_{SH} and R is given by

$$\log_{10} K_{\text{SH}} = \int 1/\alpha d \log_{10} R + A \quad . \quad . \quad . \quad (5)$$

where A is an integration constant and α can be expressed in terms of R by means of equation (4). The integral can be evaluated graphically, and the value of A can also be obtained, since K_{SH} for acetoacetic ester is known to be 2×10^{-11} .¹⁰ The values thus obtained for K_{SH} are given in the fourth column of the table. (In the case of acetoacetic acid (12) the dissociation constant refers, of course, to the —CH₃ group, and not to the —COOH.) They should differ from the ordinary experimental values by a small statistical factor, since they were obtained from statistically corrected values of R : however, in view of the approximate nature of the present calculations, it has not been thought worth while to correct them.

In two cases it is possible to compare the K_{SH} values estimated in Table I with the results of direct measurement. McEwen¹¹ has estimated the strengths of a number of very weak acids by a series of displacement reactions, and finds $pK = 19$ for acetophenone, in excellent agreement with our value of 19.2. Neither value would be expected to be more certain than a power of ten. A more direct comparison can be made in the case of acetylacetone. The dissociation constant of this compound is usually quoted as 1.5×10^{-8} , from the conductivity measurements of Guinchant.¹² This value seems improbably high, and since earlier conductivity measurements¹³ gave a value of 5×10^{-8} , it is likely that both sets of measurements were vitiated by impurities. We have therefore determined the pH of a half neutralised solution of acetylacetone at about 20° C. Measurements with a glass electrode and a Cambridge pH-meter gave $pH = 8.76$, while colorimetric measurements with phenolphthalein gave $pH = 8.78$. The ionic strength of those solutions was 0.03, so that a reasonable value for the thermodynamic dissociation constant of acetylacetone is $pK = 8.9$, in fair agreement with the value of 9.3 in Table I. There is thus a check for our calculated values at both ends of the range, which serves to confirm the assumptions made in deriving them.

It is of interest to consider the molecular interpretation of the series of dissociation constants given in Table I. If we regard the substances concerned as derivatives of acetone, the effect of the substituents in the first seven compounds is best understood as an inductive effect, and is paralleled by the effect of the same substituents in increasing the dissociation constant of acetic acid. In terms of potential energy curves, the effect of these substituents is chiefly to raise the curve for the initial system SH + B⁻, and hence to lower the activation energy. On the other hand, in the last five substances the large increase of acid strength relative to acetone is due to the possibility of mesomerism (*i.e.* alternative formal charge distributions) in the ion formed, *e.g.* the ion of acetylacetone can be written as either CH₃.CO:CH.CO.CH₃ or CH₃.CO.CO.CH:CH₃. The increase of acid strength and rate of ionisation is thus due to a lowering of the potential energy curve for the final system S⁻ + BH. In this case the effect is not paralleled in the substituted acetic acids, since the same possibilities of mesomerism do not exist: thus CH₃COCH₂COOH is only about ten times as strong as CH₃COOH, while Table I shows

¹⁰ Goldschmidt and Oslan, *Ber.*, 1900, 33, 1146.

¹¹ McEwen, *J. Amer. Chem. Soc.*, 1936, 58, 1124.

¹² Guinchant, *Ann. Chim.*, 1918, 9, 139.

¹³ v. Schilling and Vorlander, *Ann.*, 1899, 308, 200.

$\text{CH}_3\text{COCH}_2\text{COCH}_3$ to be stronger than CH_3COCH_3 by a factor of more than 10^{10} .

It is perhaps surprising that substitution involving both inductive and mesomeric effects can be included in a common relationship like equation (5), implying that the changes in rates and equilibria can be expressed by variations of a single parameter. However, it is not likely that this simplicity would extend outside a series of closely related substances. All the compounds in Table I contain the group $\text{CH} \cdot \text{CO}-$ and give ions of the structure $\text{CO} : \text{CO}-$. If we change over to a different class of pseudo-acids the relationships which we have found no longer apply. Thus for the ionisation of nitromethane the values of R , α and K_{Hg} are known,¹⁴ but do not fit into Table I.

Reactions with Hydroxyl Ions.

The variation of α with rate found for different ketones should also be detectable by varying the catalyst B^- for a single ketone, provided that a sufficiently wide range of rates could be examined. The only possibility of realising this in practice is by comparing the observed rates for hydroxyl ion with those for carboxylate ions. It is, in fact, found¹⁵ that the observed velocity for hydroxyl ion catalysis is always lower by several powers of ten than that predicted by the Brönsted relation valid for the carboxylate ions, and this agrees qualitatively with the decrease in α for increasing rate already observed when the ketone is varied. The weak point of this computation lies in the difficulty of obtaining a satisfactory quantitative measure of the basic strength of the hydroxyl ion. By analogy with the carboxylate ions $1/K_{\text{Hg}}$ has been commonly used, with

$$K_{\text{Hg}} = [\text{H}_2\text{O}^+][\text{OH}^-]/[\text{H}_2\text{O}] = K_w/55.5,$$

55.5 being the number of formula-weights of H_2O in a litre of water. This procedure is clearly open to objection, partly on account of the high concentrations involved, and partly because it connects the catalytic power of the unassociated species OH^- with the thermodynamic properties of highly associated liquid water. The same objection applies to the use of 55.5 as a measure of the acid strength of the ion H_2O^+ . It is therefore of interest to attempt a more reliable estimate of the acid-base properties of OH^- and H_2O^+ , even if such an estimate must be a very rough one.

We shall assume for this purpose that the molecules in liquid water can be divided sharply into two classes, those which are associated and those which are free, and that only the latter are relevant in estimating the basic strength of the OH^- ion. If the volume concentration of the free water molecules is $[\text{H}_2\text{O}^*]$, and their activity coefficient (referred to infinite dilution), $f_{\text{H}_2\text{O}}^*$, then the product $f_{\text{H}_2\text{O}}^*[\text{H}_2\text{O}^*]$ will be more suitable than $[\text{H}_2\text{O}] = 55.5$ in the present context. Since $[\text{H}_2\text{O}^*] < [\text{H}_2\text{O}]$, and $f_{\text{H}_2\text{O}}^* < 1$, the effect of revision will be to decrease the discrepancy with the Brönsted relation. The position is somewhat similar to that obtaining for carbonic acid, where the conventional dissociation constant is $K_{\text{H}_2\text{CO}_3} = [\text{H}_2\text{O}^+][\text{HCO}_3^-]/[\text{CO}_2 + \text{H}_2\text{CO}_3]$, while the true value is $K^*_{\text{H}_2\text{CO}_3} = [\text{H}_2\text{O}^+][\text{HCO}_3^-]/[\text{H}_2\text{CO}_3]$. As would be expected, the efficiency of the ion HCO_3^- as a basic catalyst is much less than would correspond to the value of $K_{\text{H}_2\text{CO}_3}$.^{16, 17}

¹⁴ Pedersen, *K. danske vidensk. Selsk., 1932*, 12, 1.

¹⁵ Roughton and Booth, *Biochem. J.*, 1938, 32, 2049.

¹⁶ Olson and Youle, *J. Amer. Chem. Soc.*, 1940, 62, 1027.

¹⁷ Bell, *Trans. Faraday Soc.*, 1931, 27, 797.

We consider that a probable value for the product $f_{\text{H}_2\text{O}}[\text{H}_2\text{O}^*]$ in water at 25° is 0.13 M , which is about 400 times smaller than $[\text{H}_2\text{O}] = 55.5$. This value is based upon the following considerations :—

(1) The solubility of water at 25° in six non-hydroxylic solvents with dielectric constants between 7 and 66 is close to 5 M. This has been interpreted in terms of the electrostatic energy of the water dipole, which will rapidly attain a limiting value in media of dielectric constant considerably greater than unity.¹⁷

(2) Although there are no direct measurements of activity coefficients in the above saturated solutions, freezing-point measurements of more dilute solutions of water in a number of similar solvents indicate considerable departures from ideal behaviour.¹⁸ These departures can be attributed to the energy of interaction of the water dipoles, without the formation of associated aggregates as in pure water. An estimated average value for the activity coefficient of 5 M solutions is 0.2, giving 1.0 M (in volume concentrations) as the value of $f_{\text{H}_2\text{O}}[\text{H}_2\text{O}]$ in the saturated solutions.

(3) If the dipole energy were the only important factor, we could attribute the same value to the activity of free water molecules in liquid water, again in terms of volume concentrations. However, non-polar gases such as methane, nitrogen and the rare gases are invariably more soluble in organic solvents than in an equal volume of water, the ratio of solubilities being usually in the range 4–12. This means that (relative to organic solvents) it is difficult to introduce a non-polar molecule into water, partly because it has a smaller available free space, and partly because more work must be done in making a cavity in the liquid. The same factors will operate in determining the concentration of free H_2O molecules in water, and we have therefore decreased the value of 1.0 M by a further factor of 8, giving finally $f_{\text{H}_2\text{O}}[\text{H}_2\text{O}^*] = 0.13 \text{ M}$.

We shall therefore use as a measure of the basic strength of the OH^- ion the quantity $0.13/K_w = 1/8 \times 10^{-14}$. This value is likely to be too low, since in making a sharp division between free and associated water molecules we are no doubt exaggerating the true position. However, even this large decrease in the basic strength attributed to OH^- is insufficient to reconcile the observed rates for the reaction $\text{SH} + \text{OH}^-$ with the values calculated from R and α for carboxylate ions. The values of R_{OH} given in Table I would demand a value of approximately 2×10^{-12} for the "true" dissociation constant of H_2O , which is much greater than the upper limit of 8×10^{-14} which we have obtained. We can therefore conclude that there is a real discrepancy between the observed and calculated values of R_{OH} , indicating as before a decrease in α as the velocity increases.

It is of interest to see how far this decrease in α is consistent with the relations already found between α and rate when the nature of the ketone is varied. For this purpose we shall use our revised value of $1/8 \times 10^{-14}$ for the basic strength of OH^- . Let α_{OH} be the value of α which would be observed if it were possible to study a number of bases with strengths near to that of the OH^- ion. Then if equations (3) and (4) are valid for change of base, we have for a given ketone,

$$\log_{10} \frac{10^{-4}}{8 \times 10^{-14}} = 9.1 = \int_{\alpha}^{\alpha_{\text{OH}}} \frac{1}{\alpha} d \log_{10} R = - 2.92 \int_{\alpha}^{\alpha_{\text{OH}}} \frac{\alpha}{\pi} \cosec^2 \alpha d\alpha \quad (6)$$

Knowing α , it is possible to calculate α_{OH} for each ketone by graphical integration, and the values thus obtained are given in the last column of Table I. These calculated values of α_{OH} should then be related to the observed values of R_{OH} by equation (4), represented by the straight line

¹⁸ Bruni and Amadori, *Trans. Faraday Soc.*, 1905, 5, 290.

in Fig. 1. The triangles in the figure represent the plot of $\log_{10} R_{OH}$ against α_{OH} , and are seen to fall near the line. (The numbers refer to the ketones, as before.) It seems likely, therefore, that the relatively low catalytic effect of the hydroxyl ion can be approximately accounted for without any special explanations, provided that corrections for the association of water are applied when estimating the basic strength of the species OH^- . On the other hand, if we compare the variation of R_{OH} from one ketone to another with the values of K_{SH} previously obtained, the corresponding value of α_{OH} is about 0.78, which is much higher than the values obtained from equation (6). This discrepancy is at present unexplained.

Summary.

The chief points in the above discussion may be summarised as follows :

(1) Data have been collected for the rates of ionisation of twelve ketones and similar substances in presence of bases, and for the dependence of the rate of ionisation on basic strength. Regularities have been pointed out and interpreted in terms of potential energy curves.

(2) The above data have been used to deduce approximate values for the acid dissociation constants of the ketones concerned, which range from 10^{-8} to 10^{-10} . The value calculated for acetophenone is 10^{-9} , in agreement with other experimental data. The acid dissociation constant of acetylacetone has been determined by indicator and glass electrode measurements and found to be approximately 10^{-9} , in agreement with the calculated value. The value of 1.5×10^{-6} usually quoted for acetylacetone is in error.

(3) The effect of substituents on the acid strengths of ketones has been discussed in terms of inductive and mesomeric effects.

(4) An attempt has been made to estimate the concentration of unassociated water molecules in liquid water, and hence to obtain a more reliable estimate of the basic strength of the hydroxyl ion. The latter is estimated at $0.13/K_w$, rather than the usual figure of $55.5/K_w$. (Similarly, the acid strength of the ion H_3O^+ is probably about 0.13 rather than 55.5.) Using this revised value, the rates of ionisation of ketones in presence of hydroxyl ions fall roughly into line with the other kinetic and equilibrium data, though there are still some unexplained discrepancies.

(5) The following general conclusion can be drawn from the above facts. In the reaction $\text{SH} + \text{B}^- \rightleftharpoons \text{BH} + \text{S}^-$ (where SH is a ketone) the effect upon the reaction velocity of substituents in either SH or B^- can be expressed uniquely (though approximately) in terms of their effect upon the equilibrium constant of the reaction. In other words, the effect of substituents in either reactant is primarily to alter the relative positions along the energy axis of the potential energy curves concerned, without seriously changing their shapes.

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THE ELECTRICAL PROPERTIES OF COPPER-MANGANESE-ALUMINIUM ALLOYS.

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Several different types of copper alloys are used as electrical resistance materials according to the particular application and the properties desired. Where a negligible temperature coefficient is a necessary or desirable feature of the design, as it is in resistances in voltage regulators for switchgear and other electrical plant, binary alloys containing 55-60 % Cu and 40-45 % Ni have been very generally used in recent years as resistance materials. In other applications where a zero temperature coefficient is necessary only up to relatively low temperatures, that is, about 40° C., as for standard resistances, post-office boxes and the like, alloys of the Manganin type are commonly employed. These are essentially alloys of Cu with about 12-14 % Mn and 1.5-4 % Ni. Unlike the Cu-Ni alloys they are not suitable for use at moderately elevated temperatures since under these conditions they oxidise readily and the electrical resistance alters in consequence. There are, of course, other characteristics required in resistance materials, including suitable mechanical properties, resistance to corrosion, permanence of electrical properties, amongst others. In resistances operating at temperatures between 200 and 350° C. the working conditions can generally be divided into three groups.

1. The resistance is hot for very long periods as, for instance, the continuously rated resistances in field rheostats.
2. The resistance is intermittently rated, but is heated and cooled frequently, as in constant starting resistances in automatic gear.
3. The resistance is heated infrequently, as in hand operated switches.

It is already well known that in addition to increasing the resistivity of Cu, the presence of Mn in increasing proportions decreases the temperature coefficient of the binary alloys until at 9 % of Mn it is almost zero. The addition of smaller amounts of Ni reduces the magnitude of the thermoelectric effect of the alloy against Cu, which is essential for accurate instrument work. The ternary Cu-rich alloys containing Mn and Al also possess useful and interesting properties as resistance materials, and the work briefly described in this paper was undertaken to ascertain their suitability for this purpose at operating temperatures of 200-350° C.

In earlier work Thomas¹ determined the electrical resistivities of Cu alloys containing 4 to 16 % Mn and 0 to 8 % Al and also the temperature coefficients and E.M.F. of the alloys against Cu. Most of the measurements were made on hard drawn wire, but since the softening or annealing temperature of some of the alloys may be relatively low, it is important to know their properties in the annealed condition. Moreover, the observations which Thomas made on permanence and reproducibility were limited to the range of 0-100° C. and only for short periods of time.

Preparation of Materials.—Four ternary alloys and two each of the Cu-Al and Cu-Mn binary alloys were cast as billets and ingots, from which were prepared wire and strip for various tests, the results of which are given in Tables I-III. The castings were initially hot rolled and then processed into wire by cold drawing and into strip by cold rolling further with intermediate anneals at 600-650° C.

Microstructure.—In the cast condition all of the alloys showed a microstructure of cored solid solution which became homogeneous on working

¹ J. L. Thomas, *J. Rss. Nat. Bur. Stand.*, 1936, 16, (2), 149.
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Mechanical Properties of the Alloys in Wire Form
($\sigma_0 = 64$ lb. in. δ_0 Diameter) as Annealed and as Hard Drawn.

Alloy No.	Nominal Composition.			As Annealed.*			As Hard Drawn.†			Electrical Resistivity and Temperature Coefficients of the Alloys.		
	Cr.	Mn.	Al.	Tensile Strength (tons/sq. in.).	Elongation (% on a 2 in.).	Elongation (% on 2 in.).	Tensile Strength (tons/sq. in.).	Hard.‡	Fully Annealed.*	Fully Annealed Conditions. Temperature Coefficient (per °C.) between 20 and 95 °C.		
1	95.5	—	4.5	22.5	45	49.9	4	11.15	9.83	+ 0.000792		
2	94.5	—	5.5	23.0	41	51.6	4	11.5	10.03	+ 0.000835		
3	91.0	9.0	—	21.2	42	32.2	5	34.0	33.4	+ 0.000082		
4	90.5	9.5	—	21.5	35	33.8	5	36.0	35.2	+ 0.000091		
5	94.0	5	1	22.4	46	40.2	5	21.7	21.35	+ 0.000036		
6	93.0	5	2	24.4	43	44.2	9	23.0	22.6	+ 0.0000388		
7	89.0	10	1	22.4	40	43.8	16	37.25	36.55	+ 0.0000375		
8	88.0	10	2	23.8	38	47.5	6	30.05	38.25	+ 0.0000367		

Oxidation Tests on Alloys in Strip Form.

Change in Weight, ε , sq. cm. $\times 10^{-4}$.

Alloy No.	Nominal Composition.			400° C.			500° C.			600° C.			Per Cent Change in Resistance.
	Cr.	Mn.	Al.	2 hr.	8 hr.	2 hr.	8 hr.	2 hr.	8 hr.	Initial.	Final.		
1	95.5	—	4.5	0	+ 5.0	+ 8.0	+ 7.6	+ 10.3	+ 9.8	+ 10.95	+ 0.89	0.090	1.1
2	94.5	—	5.5	+ 9.0	+ 5.0	+ 5.06	+ 5.06	+ 7.75	+ 7.4	+ 13.7	+ 0.260	0.265	1.9
3	91.0	9.0	—	+ 9.5	+ 9.5	+ 9.5	+ 9.5	+ 10.3	+ 9.8	+ 13.7	+ 0.376	0.370	1.6
4	90.5	9.5	—	+ 9.0	+ 9.0	+ 9.0	+ 9.0	+ 10.3	+ 9.8	+ 13.7	+ 0.407	0.393	3.7
5	94.0	5	1	+ 6.3	+ 6.3	+ 6.3	+ 6.3	+ 7.75	+ 7.4	+ 13.7	+ 0.460	0.462	0.5
6	93.0	5	2	+ 7.9	+ 7.9	+ 7.9	+ 7.9	+ 10.3	+ 10.3	+ 13.7	+ 0.450	0.451	0.3
7	89.0	10	1	+ 6.0	+ 6.0	+ 6.0	+ 6.0	+ 7.75	+ 7.4	+ 13.7	+ 0.750	0.745	0.6
8	88.0	10	2	+ 6.7	+ 6.7	+ 6.7	+ 6.7	+ 10.3	+ 10.3	+ 13.7	+ 0.825	0.820	0.5

*600° C.

† 50 % reduction in cross-sectional area.

and annealing. The homogenised structure consisted of the α -phase, and the grain size of the finished wires and strips varied between 0.02 and 0.04 mm., except that of the two binary Cu-Al alloys which was 0.03-0.05 mm.

Mechanical Properties.—The strengths of the wires were tested in both the annealed and the hard drawn conditions and the values of tensile strength and elongation obtained are also given in Table I. These call for little comment and show, for all the alloys, a good combination of strength with ductility.

Electrical Properties.—The specific resistances of the alloys as determined on 0.064 in. diameter wires are given in Table I in both the hard drawn (50 % reduction in cross-sectional area) and fully annealed (600° C.) conditions, together with temperature coefficients over the range of 20 to 95° C. for fully annealed wires. In preparing samples for these tests, care was taken to ensure that the annealed wires were not work hardened and that no Cu enrichment at the surface occurred as a result of annealing and pickling.

Resistance to Scaling.—It is important that alloys used for electrical resistances should possess a high degree of resistance to scaling at operating temperatures and that not only should the amount of oxidation be small, but the oxide should be adherent so that further and progressive oxidation is prevented. The characteristics of the material in this respect are usually measured by the change in weight per unit of superficial area after prolonged exposure at a given temperature in an oxidising atmosphere.

The addition of Al to Cu is known to increase the resistance to oxidation and scaling, but the binary Cu-Mn alloys scale quite readily even at moderately elevated temperatures. Samples of the Cu-Al alloys and of the ternary alloys in strip form were heated at temperatures of 400, 500 and 600° C. for periods of 2 and 8 hours and the resulting loss or gain in weight is indicated in Table I. Those alloys containing 2 % of Al or more, i.e. alloys 1, 2, 6 and 8, generally showed a slight increment in weight after two hours' oxidation, but this increment was not proportionately increased after exposure for eight hours at the same temperature, indicating that a protective film was formed at the surface which restricted further oxidation. On the other hand, alloys 5 and 7 which contain only 1 % of Al, oxidised progressively which resulted eventually in flaking of the oxide scale and loss in weight. The oxide skin formed in those alloys containing 2 % of Al and more, did not flake or even crack when the oxidised strips were bent through 180° C. These results show that the effect of Al is to produce an adherent coating or oxide scale and that in the ternary alloys, provided the Al is of the order of 2 %, there is no tendency either to crack or flake and the alloys oxidise only slightly.

Stability of Electrical Resistance at Temperatures above Normal.—All alloys used for electrical resistance purposes must be permanently stable at temperatures up to and preferably some way beyond their normal operating temperatures. Some of the factors which may affect the resistivity of wire over a period of time at moderately elevated temperatures are briefly outlined below.

(1) Annealing effects which may take place at elevated temperatures resulting in a decrease in electrical resistivity.

(2) The formation of oxide scale which increases resistivity as a consequence of the reduced cross-section of area of the conductor. Depending on the nature of the oxide skin formed, it may progressively increase in thickness, and may also, on heating and cooling, crack or flake and thus expose further metal surfaces to oxidation. On the other hand, the oxide formed may be compact and closely adherent and protect the metal against further wastage and scaling.

(3) Oxidising effects are not necessarily limited to simple scale formation and in some Cu base alloys, for example, it has been shown that oxygen

may combine with deoxidising elements in preference to the Cu, to form very fine precipitates. The formation of a sub-scale of this kind resulting from diffusion amounts to the removal of deoxidising elements from solid solution and a consequent decrease in the electrical resistivity of the alloy.

(4) Many of the alloy systems undergo phase changes in the solid state with corresponding alterations in resistivity characteristics. While the constitution of the Cu-Mn-Al alloys is not completely established, there is no evidence that the α -phase is not stable. On the other hand, it is conceivable that there could be a change in solid solubility limit, and if this were so it could affect the resistivity of the material.

Although most of the foregoing factors would result in a decrease in

TABLE II.—EFFECTS OF INTERMITTENT HEATING AND COOLING FROM ROOM TEMPERATURE TO 300 AND 400° C.

Alloy No.	Per Cent. Variation in Resistance.			
	After 1 Hour at 300° C.	After 14 Days at 300° C.	After 1 Hour at 400° C.	After 14 Days at 400° C.
7	+ 0.1	+ 0.9	+ 1.0 + 0.2	+ 3.6 + 0.2
8				

resistivity, their relative effects will vary in different materials and also according to the heating conditions. It is only possible, therefore, to obtain information concerning the stability of resistance materials at working temperatures by actual tests carried out over a period of time in which any changes in the resistivity values are noted. Several methods of testing procedure have been advocated, but the only one generally recognised in this country is that detailed in B.S. 115, clause 7, for Class C material, in which the material is heated for one hour at 450° C. and subsequently for one month at 350° C., as a result of which the resistivity must not have altered by more than $\pm 1\%$.

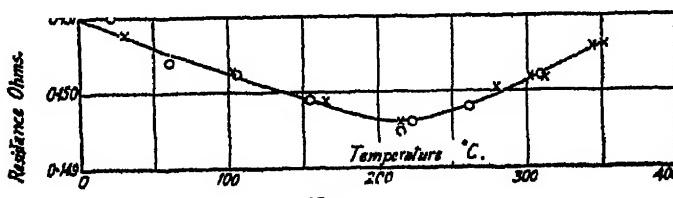


FIG. 1.

Samples of all eight alloys were subjected to this test and the results obtained are given in Table I. Both the Cu-Al and Cu-Mn binary alloys showed a change in resistivity of more than 1% after this treatment, but the change in resistance of all four of the ternary alloys was well below 1%.

In many applications electrical resistance alloys are not exposed continuously to heating, but are subjected to intermittent heating. Some intermittent heating tests simulating service conditions were, therefore, carried out on alloys 7 and 8 to obtain some indication of the tendency of the oxide coating to flake off and the effect on resistivity values. The test comprised heating specimens of wire at 300 or 400° C. for three hours,

followed by one hour at room temperature, and this cycle of intermittent heating and cooling was repeated for a period of a fortnight. The results obtained are given in Table II, from which it will be seen that the stability of the alloy containing 10% Mn and 2% Al is satisfactory after intermittent heating of this kind.

The temperature coefficient of electrical resistivity for this alloy was determined over the range 20-350° C. and the results are given in Table III and plotted in Fig. 1. The temperature coefficient first decreases with rising temperature and then increases so that the temperature coefficient of resistance is about -0.000045 between 20 and 200° C. and +0.00005

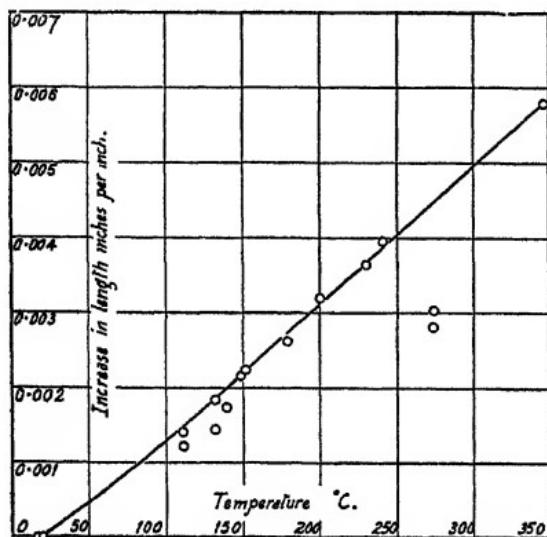


FIG. 2.

between 200 and 350° C., the net effect being a negligible change in resistance between 20 and 350° C.

TABLE III.—COEFFICIENT OF ALLOY 8 UP TO 350° C.

Temperature Rising.

Temp. °C.	R. (Ohms).	Temp. Range.	α Per °C.	α from 0-350°.
31	0.15078	—	—	—
102	0.15020	31-102	-0.000040	—
105	0.14984	102-105	-0.000042	—
215	0.14950	105-215	-0.000044	-0.0000072
302	0.15020	215-302	+0.000053	
350	0.15062	302-350	+0.000058	

Temperature Falling.

310	0.15021	310-262	-0.000057	+ 0.0000072
262	0.14980	262-213	-0.000045	
213	0.14947	213-155	+0.000048	
155	0.14989	155-107	+0.000050	
107	0.15025	107- 21	+0.000065	
21	0.15110			

Linear Coefficient of Expansion.—The linear coefficient of expansion of a resistance material is also an important property since if this is excessive, loosely wound spirals not supported on formers may buckle

unduly and cause shorting and arcing. The expansion of the 10 % Mn, 2 % Al alloy between 20 and 350° C. is shown in Fig. 2, from which it will be noted that it is practically a linear function of temperature, the coefficient of expansion being 0.0000175° C. This value is about normal for resistance materials and should not, therefore, lead to any difficulties due to thermal expansion when in service.

The authors' thanks are due to Imperial Chemical Industries Limited for permission to publish the results contained in this paper.

The Faraday Society

Minutes of Special General Meeting

A Special General Meeting of the Society was held at the Hotel Rembrandt, South Kensington, London, S.W.1 on the 24th September, 1943, at 5 p.m.

The Secretary announced that the meeting was held in accordance with the wishes of members expressed at the Thirty-Sixth Annual General Meeting held on the 12th December, 1942, at the Hotel Rembrandt, London, S.W.1.

The President reported briefly upon the present position of the Society. The Council had not found occasion to meet very frequently, its main business being to arrange for the General Discussions and to elect new members. The membership continued to grow. There had, of course, been a drop in the early days of the war owing to the fact that a considerable number of members became enemies and, in the circumstances, the Council did not think fit to exercise its discretion under rule 15 to continue the membership of the enemy members whose subscriptions were in arrears. The present membership is about eight hundred.

The Council had been engaged in negotiations with representatives of the Chemical Council as to the possibility of the Society co-operating more closely with other chemical societies. The Council felt, however, that in view of the large proportion of its members who are primarily physicists rather than chemists, and in view also of the large number of members who are not resident in the British Isles, the Society's interests would be best furthered by seeking, in co-operation both with chemical and physical societies, in this country and abroad, to improve physico-chemical abstracts. The Council contemplate the possibility, if such arrangements can be made, of securing such abstracts for members.

The Council had also considered what advice they should give to the members in connection with the next item on the Agenda. The Secretary said that the unanimous opinion of the Council was that the President should continue in office in view of the fact that he was actively engaged in the negotiations with other Societies to which the President had referred in his opening remarks, and that a proportion of the Vice-Presidents and Ordinary Members of Council, namely one-third, should retire so that the pre-war practice for the election of the Council should in that respect be restored.

The meeting then unanimously adopted the above suggestions with regard to the election of Council at the forthcoming Annual General Meeting.

With regard to the Presidency, the meeting was unanimously of opinion that the President should continue in office for such time as the Council should think fit, and that the choice of the retiring one-third of the Vice-Presidents and Ordinary Members of Council should be determined by seniority of office, whilst paying due attention to the desirability of maintaining on the Council those members who were in a position to attend meetings. Accordingly it was unanimously decided that the new rule 20^{*} which was passed at the Special General Meeting held on the 9th January, 1941, as follows :—

" During the present war, those provisions of Rules 19 and 20 whereby the President, Vice-Presidents and ordinary Members of Council are not eligible to hold office for more than the periods in those Rules mentioned shall cease to have effect."

should be amended to read as follows :—

" During the present war or for so much thereof as the Council may so decide, Rule 19, whereby the President is not eligible to hold office for more than two years, shall cease to have effect."

Arising from the President's report the meeting suggested that local secretaries of the Society should be appointed in various parts of the country in order to promote membership of the Society, and that to that end professors of physical chemistry at the various universities should be invited to ask some active member of the staff to undertake this duty. The meeting also asked the Council to consider whether steps might not be taken to invite the organisers of local symposia, which from time to time are held at the universities throughout the country, to be held in connection or under the ægis of the Society.

This concluded the business of the meeting.

CORRIGENDA.

P. 186, l. 9. *For Fig. 1 read Figs. 1 and 2.*

P. 186, l. 7 from bottom. *For $x - (c + \alpha F)/w$ read $x - (c + \alpha F)/w$.*

P. 189, l. 9 from top. *For $x - c_x - (1 - c_s)X_w$ read $x - c_x - (1 - c_s)X_u$.*

THE FAST AND SLOW EXTENSION OF SOME PLASTIC MATERIALS.*

By R. N. HAWARD.

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Introduction.

In an earlier paper³ some extension and breaking experiments on cellulose acetate and celluloid were described and empirical equations were used to describe the experimental results. These were then considered in the light on the known high toughness of the materials, and it was concluded that, if a tough stiff material was required, it must extend at high or moderate stresses at a rate which increases very rapidly with increase of stress. It must also be capable of quick rupture only under stresses markedly higher than those at which the rates of extension are readily measurable.

The essential assumption underlying this approach is that, apart from adiabatic and isothermal differences, there is no qualitative distinction between slow extension and deformation under impact. The difference is purely one of time.

If we could obtain two equations, one describing the extension and the other the rupture of a material under all conditions, then the results of all the varied impact and flexibility tests would become, at least in theory, predictable.

We will now consider the case of a material whose properties are generally similar to those we have found for the two cellulose derivatives and subject it to an idealised impact. We may write $\sigma = \Sigma + \text{Hookean Strain}$, also $\Sigma = \Sigma(S_0, t)$ and $\frac{d\Sigma}{dt} = \Sigma'(S_0, t)$, where $\Sigma \rightarrow A$ as $t \rightarrow \infty$, and $\frac{d\Sigma}{dt}$ has a maximum value at a given time $(\frac{d\Sigma}{dt})_{S_0}^{(\max)}$. The Hookean Strain, on the other hand, is time independent and $= S_0/E$.

* Note on Nomenclature :—

As at least two sets of symbols have been used in this field, it is considered desirable to list them at the beginning. The symbols used here are derived from the Scott Blair-Coppens equation,¹ but where they have the same meaning as those used by Tuckett,² the latter are given in brackets :—

σ , (D) . Total Strain.

$t(t)$. Time.

$\Sigma(D_{HE})$. The non-ideal elastic part of the total strain.

S_0 . Stress at any time calculated as an initial stress with original cross-section.

P_0 . Initial Cohesive Strength.

A . The Empirical Limit to Σ (in some cases the same as $D_{HE} \infty$).

β' , k' .[†] Indices of S_0 and t respectively in an equation relating ΣS_0 and t .

ψ . A constant in the same equation.

V_1 . The Critical Impact Velocity \sim the highest rate of non-ideal elastic strain.

$E(G_{ox})$. The Young's Modulus of Elasticity.

¹ Scott Blair and Coppens, *J. Soc. Chem. Ind.*, 1941, 60, 635; *P.R.S.B.*, 1939, 128, 109.

² Tuckett, *Trans. Faraday Soc.*, 1942, 38, 310; 1943, 39, 158.

³ Haward, *ibid*, 1942, 38, 394.

[†] Dr. Scott Blair has pointed out that my constants β' , ψ , and k' differed from those which he and others had used in that in my case, the Hookean Extension had been subtracted from the total extension. It would therefore appear desirable to mark them β' , ψ' and k' to avoid possible confusion.

With regard to the breaking of the material we assume that the breaking time is given by $t = t(S_0)$ such that as $t \rightarrow 0$, $S_0 \rightarrow P_0$, P_0 being called the Initial Cohesive Strength ‡ and is the highest stress to which the material may be exposed without immediate rupture.

In the idealised impact, we subject a piece of this material of length L and unit cross section to extension at velocity V by the action of a heavy body acting on a rigid system, i.e., V does not vary perceptibly as work is absorbed.

While the material is extending

$$V = L \left(\frac{d\Sigma}{dt} + \frac{1}{E} \cdot \frac{dS_0}{dt} \right)$$

i.e., if $\frac{d\Sigma}{dt} < \frac{V}{L}$, $\frac{dS_0}{dt}$ will be positive. Hence S_0 will rise steadily until it exceeds P_0 when rupture will occur. Under these conditions the non-ideal elastic extension will be smaller than, or comparable with, the Hookean extension, and for this purpose it is sufficient that

$$\left(\frac{d\Sigma}{dt} \right)_{P_0}^{(\max)} \text{ the highest possible value of } \frac{d\Sigma}{dt} < \frac{V}{L}.$$

If, however, $\frac{d\Sigma}{dt}$ becomes $> \frac{V}{L}$ then dS_0/dt becomes zero or negative, i.e., there will be constant or even decreasing stress, and Σ may become very large. For this purpose it is necessary but not always sufficient that $\left(\frac{d\Sigma}{dt} \right)_{P_0}^{(\max)} > \frac{V}{L}$.

In general if Σ becomes large it will be limited not by the time factor but by the extension limit A which appears to be a general property of the non-ideal elastic extension. In this case, there will be an upper limit to the work taken up, which may be called the Ideal Total Work and is given by the sum of the Ideal Hookean and non-ideal elastic work, each taking place at P_0 , the maximum initial stress. Since the Hookean work equals $\frac{1}{2} \frac{P_0^2}{E}$ we may write

$$\frac{1}{2} \frac{P_0^2}{E} + P_0 A = \text{Ideal Total Work.}$$

We may conclude that the contribution of the non-ideal elastic extension during impact is limited by three quantities, namely,

(1) The velocity of impact must be less than a Critical Impact Velocity V_i which will be of the same order as $\left(\frac{d\Sigma}{dt} \right)_{P_0}^{(\max)}$ and will have the dimensions of $\frac{I}{T}$ (cf. angular velocity).

(2) There will be a corresponding highest rate of energy absorption roughly given by $\left(\frac{d\Sigma}{dt} \right)_{P_0}^{(\max)} \times P_0$.

(3) The total energy cannot exceed the product $P_0 A$ in the Ideal Total Work.

We may note that both the critical impact velocity and the Ideal Total Work are idealised quantities which are not necessarily absolutely invariable for a given material, but they can still be valuable in explaining apparent inconsistencies in the behaviour of materials under impact. For instance, the limit A may vary slightly with the initial stress, but

‡ The term "Initial Cohesive Strength" is substituted for "Snapping Strength" as the term is clearly related to the conception of cohesive strength as applied to metals (Hoyt, A.S.T.M., 1938, 38, 153).

the difference between the value of 0.5 for cellulose acetate and at least 7.3 for rubber^{4, 5} is large enough to give rise to significant conclusions even if each of these quantities was subject to a variation of $\pm 50\%$.

Similarly the Critical Impact Velocity may be fixed within an experimentally significant range. This has been done by Myers⁶ who measured it in arbitrary units by finding the critical range of velocity in which a flywheel impinging on a sheet of plastic causes a change-over from bending to breaking. He claims that this velocity is a measure of toughness whose value is confirmed by experience. His results show that for his materials the rate factor is decisive. However, he notes that he cannot find any correlation between his bending experiments at high velocities and the properties of the materials under slow extension.

In this paper experimental results on the slow extension and breaking of cellulose acetate and poly-methyl methacrylate films will be presented, and, in the case of the former, an investigation of the change in properties with temperature will be included. In this way the limited nature of the effects due to adiabatic conditions can be illustrated, and tentative conclusions regarding the possible behaviour of these materials under impact conditions deduced. These are compared with the results of some simple impact experiments and it is concluded that, when the various factors outlined in the foregoing discussion are taken into account, apparent contradictions between slow and fast extensions can be eliminated. Naturally it is realised that the correctness or otherwise of the views expressed above can only be satisfactorily demonstrated when a full picture of the rates of extension of a number of materials under a very wide range of conditions becomes available. In the absence of such full information the results of more limited experiments can be usefully considered.*

⁴ Boggs and Blake, *Ind. Eng. Chem.*, 1936, 28, 1198.

⁵ Igmanson and Kemp, *ibid.*, 889.

⁶ Myers, *Modern Plastics*, 1942, 20, Oct., p. 81.

* Note on the Assumptions involved in the above Discussion:—

(1) $d\Sigma/dt$ increases as the stress increases and, at a given stress, has a maximum value at a given time. This applies to all extension curves measured, but when a material is extended under constant load with decrease of cross-section $\left(\frac{d\Sigma}{dt}\right)_{S_0}^{(\max)}$ may or may not be at $t = 0$. Under constant stress this would normally be anticipated.

(2) The Ideal Hookean extension has no time factor. This is by definition (*cf.* British Rheologists' Club, *Nature*, 1942, 149, 702). Little is known as to whether the Hookean extension of a plastic material as defined by its (Young's) Modulus of elasticity has a practically measurable upper limit of velocity. Since this type of deformation is involved in the transmission of sound it would appear to be capable of taking place fairly quickly.

(3) The breaking time curve is asymptotic to P_0 at short times. This appears to be the best assumption on the available evidence. The existence of a critical head speed for tensile testing, above which no further increase of strength occurs, has been put forward by Couzens and Wearmouth⁷ and Findlay.⁸ Further evidence is given in this paper.

(4) That times long enough for condition (2) are short enough for $S_0 \sim P_0$ during the non-ideal elastic extension. Only approximate agreement is assumed here in deriving the Ideal Total Work, which is a maximum quantity. The Theory also takes no account of changes of strength during elongation which might lead to values of the strength greater than P_0 .

(5) All the extension experiments and the equations derived are based on a constant initial load, S_0 . Under impact conditions the stress S will naturally vary with time. It is assumed that this will not introduce differences so great as to cause the analogy between the two types of extension to break down.

⁷ Couzens and Wearmouth, *J. Soc. Chem. Ind.*, 1942, 61, 69.

⁸ Findlay, *Modern Plastics*, 1941, Sept., p. 57.

The Fast and Slow Extension of Real Materials.

The general technique of the extension experiments whose results are presented here is the same as that described in an earlier paper.³ A strip of film was extended at a given temperature under constant load and a series of such extensions carried out at different initial loads to give a family of total extension-time curves. A complementary series of experiments on suitable test pieces then enables the time of rupture at any given initial stress to be measured and the corresponding logarithmic breaking-time curves plotted. These include results at quite short times and, no doubt, also include small adiabatic effects. The extension curves, on the other hand, are confined to rates of extension where isothermal conditions may be reasonably anticipated. As a consequence, predictions concerning fast extensions can only be reached by means of a long extrapolation

of the results, which is clearly shown in the form of presentation adopted. Such an extrapolation is, of course, involved in all attempts to relate slow and fast extensions, and can only be eliminated when extension-time curves are available over the whole range of extension rates.

Comparison of Polymethyl Methacrylate and Cellulose Acetate Films.

Isothermal extensions under constant load can be made with plasticised methacrylate [†] films in the manner outlined above and total extension-time curves obtained. A family of such curves at a series of stresses for a methacrylate film containing 25 % dibutyl phthalate is given in Fig. 1 together with a typical cellulose acetate extension. The outstanding difference between the

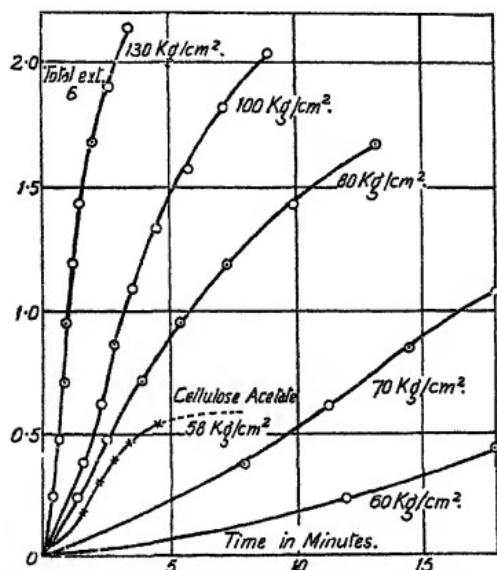


Fig. 1.—Strain-time curves for polymethyl methacrylate 25 % dibutyl phthalate 26° C. A typical cellulose acetate curve is included for comparison.

deformation properties of the two materials is at once obvious. Clearly the extension limit of the methacrylate films is very much larger than that of the cellulose acetate. Taken alone, this property would suggest that methacrylate should have a higher value of the Ideal Total Work than cellulose acetate and would tend to be "tougher"—a conclusion contrary to experience.⁴ However, if we assume that the weakness of methacrylate is due to factors connected with the critical impact velocity,

[†] A viscous partly polymerised mixture of methyl methacrylate containing 0.5 % benzoyl peroxide and a known quantity of plasticiser was completely polymerised between glass plates at 60° C. and finally dried out for 24 hours at the same temperature. The intrinsic viscosity (Gee, *Trans. Faraday Soc.*, 1940, 36, 1167) of the polymeric material varied between 1.5-2.0. Unless otherwise stated extensions were carried out at 26° C. and 33 % humidity.

* Axilrod and Kline, *J. Res. Natl. Bur. Standards*, 1937, 19, 367.

then this apparent contradiction can be reconciled and the slow extension properties become consistent with accepted experience.

For this purpose it is necessary to compare the rates of extension of the two materials together with the breaking time curves rather than the extension-time curves. It follows from the empirical treatment applied to cellulose acetate³ that if the log rate of extension-log stress curves at a given extension and a series of stresses were plotted and this procedure repeated at several different arbitrary extensions on the extension-time curve, a series of parallel lines would be obtained whose slopes were β/k' . Obviously one of these lines—that taken from the steepest part of the extension-time curve—will represent the highest rate of extension of which the material is capable at a given initial stress. It will therefore correspond with $(\frac{dE}{dt})_{\text{max}}$ discussed above. The same treatment

can then be applied to the corresponding curves obtained from methacrylate to give an empirical logarithmic line describing the highest rates of extension at a given initial stress. In this case the parallelism, within experimental error, of lines taken at other degrees of extension can be demonstrated though no attempt has been made to embody these results in an empirical relation.

The logarithmic lines of maximum rate of extension for the two materials are given in Fig. 2 together with the appropriate breaking-time curves, which are plotted against the same scale of log stress with their own log

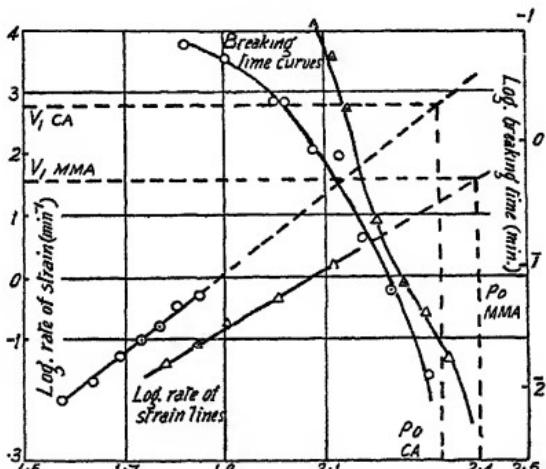


FIG. 2.—Log rate of strain, log breaking time curves plotted against the same scale of log stress. The intercepts on the left represent the extrapolated highest rates of non-ideal elastic strain.

Cellulose acetate marked ○.

Polymethyl methacrylate marked △.

time scale on the right. It will be seen that the rates of strain for cellulose acetate are everywhere greater than those for the methacrylate film and that the tendency is for the lines to diverge at higher stresses. In order to compare the extrapolated highest rates of strain or critical impact velocity, we must produce the rate of strain lines until they meet the respective P_0 asymptotes, which are the highest stresses to which the materials may be respectively subjected. The strain velocity at this point represents the extrapolated critical impact velocity and is marked V_1 on the graphs. It will be seen that the value obtained for cellulose acetate is about 10 times greater than that for methacrylate. Here it must be emphasized that no suggestion is made that the figures obtained in this way, using such a long extrapolation, are quantitative. It is only concluded that, if the extensions of the two materials are dealt with in terms of rate and strain, instead of amount of possible strain, the apparent inconsistency between slow extensions and the results of impact experiments disappears. Nevertheless, these slow extensions also indicate that, if methacrylate and

cellulose acetate can be tested under conditions in which the non-ideal extension of the methacrylate does take place, then the former should absorb the more work.

Effect of Different Quantities of Plasticiser.—In order to demonstrate the effect of plasticisers on mechanical properties the experiments described above have been repeated with two other methacrylate films containing 22% and 28% dibutyl phthalate respectively, and the results are shown

in Fig. 3. The softening effect of the plasticiser is clearly demonstrated both in the logarithmic rate of extension lines and in the breaking-time curves, which in this case also give more satisfying evidence of the existence of a real Initial Cohesive Strength than in Fig. 2. In particular, the rate of extension at low stresses is markedly increased by addition of plasticiser, but the logarithmic lines appear to converge at higher stresses and the resulting increase in extrapolated Critical Impact Velocity is not very large. Indeed, the values ob-

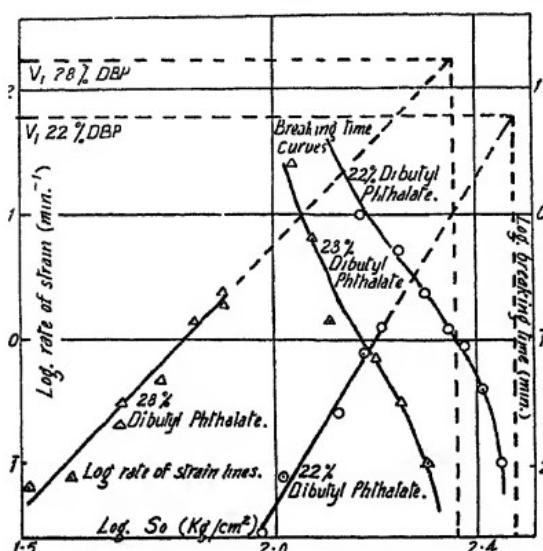


FIG. 3.—Log breaking time, log rate of strain. Curves for two plasticised methacrylates.

tained for 25% and 22% dibutyl phthalate are not substantially different, but the higher values obtained with 28% plasticiser may be significant in view of the similarity of the materials being compared. It will be shown later that an increase in plasticiser content can cause an increase in the energy absorbed during a simple impact test.

The extension-curves from which these points are derived all show a high extension limit as in Fig. 1.

The Adiabatic Effect.

(1) **The Variation in the Properties of Cellulose Acetate with Temperature.**—When a material absorbs work adiabatically its temperature will change. Therefore, the first condition for estimating the difference between an adiabatic and isothermal deformation is that of measuring the effect of temperature on the mechanical properties of the material. In the first place, our attention can be confined to the non-ideal elastic part of the extension since this alone is concerned with large energy absorption and heat changes. Although temperature coefficients in the ideal Hookean elasticity are not without interest in themselves, their presentation may conveniently be deferred.

In order to investigate the effect of temperature on the extension and rupture of cellulose acetate, a fresh batch of material was subjected to extension and breaking tests at 20, 26, 33 and 40°C. The extensions were then submitted to the empirical treatment given in the earlier

paper³ and it was found that at 40° C. this method broke down * but at the other three temperatures a fair representation of the results could be obtained. However, apart from the extension limit A which did not diverge appreciably from 0.5 at the three lower temperatures, all the constants varied with temperature. For the above reasons, no attempt is made in Fig. 4, where these results are given in the same form as Figs. 2 and 3, to plot a logarithmic highest rate of extension line for the experiments at 40° C. The results at other temperatures show that the effect of raising the temperature of cellulose acetate is similar to that of increasing the plasticiser in methacrylate films. The material extends more easily and breaks more quickly at low stresses, but at high stresses these differences tend to diminish.

It may therefore be concluded that when a material like cellulose acetate undergoes a non-ideal adiabatic extension it will extend a little faster at a rather lower stress because of the heating effects involved, but that the differences introduced by adiabatic conditions will not be very large unless the rise in temperature is considerable. This, however, only refers to the effects of temperature change during an extension in which a fair amount of work is already being taken up. It does not apply to the effect of initial temperature on total work absorption and cannot do so since these extrapolated curves furnish no indication of the effect of temperature on critical impact velocity. On this point, the direct impact experiments of Callendar,¹⁰ the bending experiments of Kemp, Malm and Winspear,¹¹ and the figures in Table II, show that large increases in work absorption or rates of extension with rising temperature, are common. It is therefore concluded that V_1 normally increases with the temperature.

(2) Estimation of the Possible Temperature Changes During Extension.—In the last section it was suggested that if adiabatic temperature rises were to have an important effect on extension properties, they would have to be large. Their magnitude is now considered quantitatively.

In the first place, however, it must be noted that during the ideal Hookean extension there will be a slight cooling effect. In this type of deformation plastics behave in a similar way to metals (*cf.* Joule¹²) as

* The deviations could be partially represented by allowing A to vary with stress, but no evidence of permanent plastic flow could be obtained. One out of the six extensions at 33° also failed to fit the empirical treatment in a satisfactory way.

¹⁰ Callendar, *Brit. Plast.*, 1942, 13, 445, 506.

¹¹ Kemp, Malm and Winspear, *Ind. Eng. Chem.*, 1943, 38, 448.

¹² Joule, *P.R.S.*, 8, 335, 1857; *Phil. Mag.*, 14, 226, 1857.

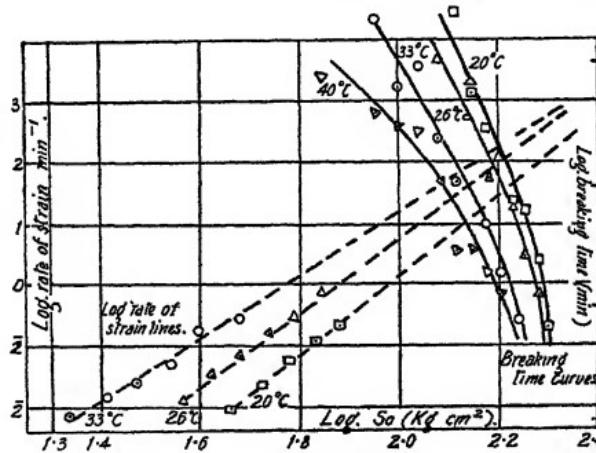


FIG. 4.—Log rate of strain, log breaking time. Curves for cellulose acetate at different temperatures.

was shown by McNally and Sheppard¹⁸ in an investigation of the thermal effects during the extension of cellulose acetate and nitrate. They found that there was a distinct initial cooling effect which changed to a larger heating effect at the "yield point," i.e. the point at which the non-ideal extension began to take place. In the case of a highly plasticised material like the cellulose acetate described here, the relative magnitude of the non-ideal extension will be greater than that in the plastics investigated by Sheppard and McNally. In the subsequent discussion this cooling effect is neglected.

In order to evaluate the total temperature change in a material during sudden non-ideal extension it is necessary to know the specific heat, the specific gravity of the material, and the amount of work absorbed. The determination of the first two quantities is straightforward but the last one will depend on the conditions of testing. We can, however, use our figure for the non-ideal part of the Ideal Total Work, viz., $P_0 A$, which is the highest amount of non-ideal work the material can absorb, to give an upper limit to the possible rise in temperature.

This is shown in Table I.

Since, in practice, the temperature rises will be less than these, it seems fair to conclude that differences between isothermal and adiabatic extensions will not play a very large part in causing differences between fast and slow deformations of these materials.

attention has been directed

The Ideal Hookean Extension.—So far attention has been directed to the non-ideal elastic extension, because it is the larger source of deformation and also because of the importance of the time factors associated with it. However, the Hookean extension has a special importance because it is an ideal, i.e. quick, time-independent deformation. This gives it the property of being always available under normal conditions of impact and therefore a universally applicable source of flexibility and toughness. For this reason, the values of the Young's Modulus E , the maximum Hookean strain P_0/E and of the Hookean work $\frac{1}{2}P_0^2/E$ may be compared for varied materials without further qualification, to give an indication of their possible toughness. Such a list is given in Table II.

The most interesting point about this table is the degree to which the highest extension and Hookean work actually corresponds with ordinary experience of flexibility and toughness. There may be two reasons for this. Firstly, that the Ideal Hookean extension is the one involved in ordinary methods of handling, and secondly, the Hookean extension plays a dual role in energy absorption, not only taking up work itself but also giving the non-ideal deformations more time to take place. In this way a large Hookean extension may help to compensate for a low Critical Impact Velocity; at the same time, the non-ideal extension must play the dominant part where any very large absorption of energy takes place.

Surface Effects on Impact Testing.—Since the Hookean work taken up by a material is given by $\frac{1}{2}P_0^2/E$, it follows that for any material whose work absorption is mainly of the ideal Hookean type and which is treated in such a way as to alter P_0 and not E , the relation

$$\frac{\text{Initial Cohesive Strength}}{\text{Impact Strength}}$$

¹⁸ McNally and Sheppard, *J. Physic. Chem.*, 1931, 35, 100.

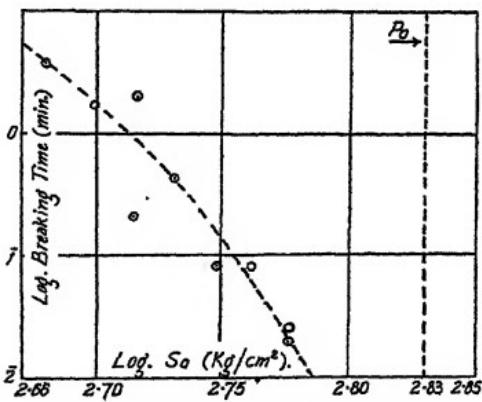
TABLE II.—THE YOUNG'S MODULUS AND RELATED QUANTITIES FOR SOME PLASTIC MATERIALS AT 26° C.

Material.	Young's Mod. (E).	P_0 .	Highest Extension.	Work = $\frac{1}{2}P_0^2/E$.
Cellulose acetate ^a	2,400 Kg/cm. ^b	210	0.09	9 Kg. cms./c.c.
Celluloid	19,100 "	(680) ^b	0.04	1.2 "
Polymethyl methacrylate ~ 25 % dibutyl phthalate	5,700 "	250	0.04	5.5 ..
Ditto. 22 % D.B.P.	7,300 "	300	0.04	6 ..
Phenol formaldehyde, ^c 60 mins. at 150° C. (C stage)	59,500 "	670	0.01	3.8 ..
Cresol formaldehyde ^c (same as above)	50,000 "	330	0.007	1.1 ..
Urea formaldehyde, ^c (cast C stage)	31,000 "	300	0.01	1.4 ..
Glass	700,000 "	(840) ^d	0.001	0.5 ..

NOTE.—^a Haward.³^b An uncertain value (see Fig. 5) upon which the estimation of P_0 is based.^c The values for the thermosetting resins are taken from R. Houwink,¹⁴ P_0 being taken simply as his tensile strength. The actual Initial Cohesive Strength may be higher, but for such hard materials probably not much higher.^d The figures for glass were obtained from bending experiments on commercial sheet with diamond cut edges in compression. It is not a real value of P_0 which may or may not exist for glass.

should be constant. This relation should apply, therefore, to variations in impact strength brought about by surface cracks and the like, provided that the material is hard enough to ensure the substantial absence of non-ideal deformations under impact.

It would appear that "Plexiglas," whose tensile strength rises to nearly 14,000 lb./sq. in. ~ 1,000 Kg./cm.², is such a material. Figures and graphs for the effects of surface treatment on Plexiglas are given by Bartoe.¹⁵ If it is assumed that the Initial Cohesive Strength of this material is proportional to the flexural strengths measured, then, for a series of different surface treatments, the relation

FIG. 5.—Breaking time curve for celluloid.
N.B.—At lower stresses the results are even more irregular.

$$\frac{(\text{Flexural Strength})^2}{\text{Charpy, Unnotched Impact Strength}} \sim \text{Constant.}$$

¹⁴ Houwink, *Elasticity, Plasticity and the Structure of Matter*, Camb. Univ. Press, 1940, p. 155.¹⁵ Bartoe, *Aviation*, 1943, Jan., p. 128.

The figures for this relation are given in Table III.

TABLE III.

Surface Treatment.	Impact Strength (ft.-lb.) (a).	Fractural Strength lb./sq. in (b).	$\frac{b^2}{10^6}$ (a).
1. Polished to remove scratches . . .	3.2	13,750	59
2. Belt sander at 45° . . .	3.0	12,800	54
3. Belt sander perpendicular to length . . .	1.6	9,530	57
4. Same as 3 but coated with plexiglas solution . . .	2.2	13,000	76
5. Belt sander parallel to length . . .	3.5	13,500	52
6. Tension side sander perp. Compression side parallel . . .	1.6	9,300	54
7. Scratched 0.100 inches deep . . .	0.35	5,350	84
Scratched 0.050 inches deep . . .	0.45	5,550	68
Scratched 0.025 inches deep . . .	0.67	6,050	56
Scratched 0.020 inches deep . . .	0.74	6,100	50
Scratched 0.009 inches deep . . .	1.94	13,200	90

It will be seen that, although agreement is only approximate, the figures are generally favourable to the views expressed.

The Effect of Temperature on the Young's Modulus.—The values of the Young's Modulus of ideal Hookean elasticity at different temperatures

TABLE IV.—THE YOUNG'S MODULUS FOR CELLULOSE ACETATE AND CELLULOID

Temperature.	20° C.	26° C.	33° C.	40° C.	
Cellulose acetate, standard fibestos "C" . . .	4,000	3,000	1,900	—	Kg./cm. ²
Celluloid . . .	—	19,100	—	16,700	"
Rhodoid. Commercial acetate sheet . . .	—	8,400	—	7,400	"
Cellulose triacetate, 40 % butyl phthalyl butyl glycolate . . .	—	8,200	—	6,900	"

for our standard cellulose acetate, celluloid and two other less highly plasticised cellulose acetates are given in Table IV.

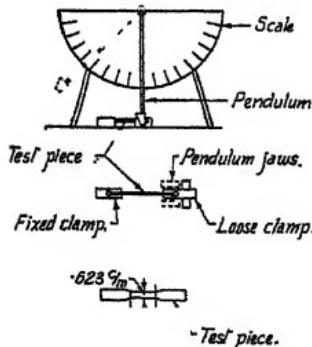


FIG. 6.—Diagram illustrating the pendulum used for the fast extension of small test pieces.

¹⁶ Tuckett, S.C.I. Plastics Group—Faraday Soc. Symposium, London, Feb. 1943. In the press.

It will be seen that E falls as the temperature is raised, but that with the harder materials, the changes are not large. These therefore fall in line with the view that the ideal elastic type of deformation is not strongly affected by temperature changes.¹⁶ In the case of the softer material it is possible that a small part of the non-ideal extension becomes very quickly reversible at higher temperatures and is therefore included in measurements intended only to cover the ideal Hookean deformations. In general the region of the borderline between the ideal and the non-ideal extensions has not been thoroughly examined in these experiments.

The differences between these figures

and those previously given³ are due to the use of fresh materials. The cellulose acetate here is identical with that used in Fig. 4.

The Measurement of Fast Extension.—One of the disadvantages of most impact tests from the theoretical point of view lies in the complexity of the geometric conditions involved. They could only be related to the known mechanical properties of materials by carrying out very difficult and complex integrations. For this reason a simple pendulum was set up which could be used to extend a simple test piece along its length with a known velocity. It is illustrated in Fig. 6.

Experimental.

The test piece was attached to two light clamps, one of which could be fixed firmly to the base of the pendulum stand and the other fitted with two side arms which engaged the arm of the pendulum as it fell. In use, three or four experiments were carried out with the test piece in position and a similar number with the clip alone. The difference in the energy taken up in the two groups gave that due to the test piece and it could then be calculated in terms of Kg.-cm. per c.c.m. of test piece, assuming that only the thin part of the test piece took part in the extension. This assumption, together with the probability of energy being dissipated through the clip and pendulum arm, means that the results obtained will be maximum values. However, even with this limitation they have a considerable interest.

TABLE V.—THE WORK ABSORPTION OF MATERIALS SUDDENLY EXTENDED BY A PENDULUM AT DIFFERENT VELOCITIES IN KG. CM./C.C.

Materials.	Reduced Velocity of Impact. cm./sec. per c.m. of test piece, i.e. sec. ⁻¹ .			
	62.	93.	180.	250.
Cellulose acetate, 130° C. .	160	130	—	130
Methyl methacrylate .	10-20 *	10-20	—	—
25 % D.B.P. 12° C. .	230	170	20	20
31·5 % D.B.P. 8-9° C. .	—	260	260	250
31·5 % D.B.P. 14° C. .	133	116	84	84

* 45 sec.⁻¹ not 62 sec.⁻¹.

Most of the figures in Table V illustrate the characteristic property of these materials of absorbing more energy as the rate of extension is decreased. In one case only (methyl methacrylate 31·5 % dibutyl phthalate 8-9° C.) is there a sharp transition from a low energy absorption to a high one. This is partly because of the limited range of the pendulum, but it is not to be assumed that all materials show such a transition. Indeed, the figures for celluloid indicate that it is equally possible for the work absorption to increase steadily as the velocity is reduced, a property which may be due to the operation of either or both of two causes. Firstly, there is a high value of the Ideal Hookean Work, which allows of varying non-ideal extensions while it is being taken up, and secondly, unlike those for methacrylate or cellulose acetate, the strain-time curve of celluloid is markedly convex and shows no increase in rate of extension as the strain increases. It could, therefore, easily be assumed to break at any point after the initial impact. In such a case V_i could only be defined within a certain range of velocities.

The results obtained from the pendulum extensions must be examined not only from the qualitative but also from the quantitative angle, with a view to finding how they compare with the predictions from slow extensions. Such a comparison is given in Table VI.

Clearly the values for the Critical Impact Velocity, based on extrapolation from slow extensions, are quantitatively wrong by at least a factor of ten. At the same time the qualitative prediction of a higher critical velocity for cellulose acetate than methyl methacrylate is confirmed.

Somewhat more importance attaches to the actual values for the energy absorbed. Here, the high degree of work absorption, which was predicted from the high extensibility of methacrylate, is actually found. The figures for celluloid and cellulose acetate also fall well within their possible values having regard to the maximum character of the results given by the pendulum. It is therefore concluded that the conception of Ideal Total Work offers a basis for relating the quantities of work taken up by various materials when tested under the most favourable conditions.

A Falling Bolt Impact Test.—A common type of test is that in which a falling object is allowed to impinge on a piece of material and the height where piercing or breakage occurs is determined. Such a test, though geometrically more complex than the pendulum, has a certain advantage in that the energy is transmitted directly to the material without intervention of moving parts.

TABLE VI.—COMPARISON OF IMPACT PROPERTIES OBTAINED BY DIRECT EXPERIMENT AND BY EXTRAPOLATION FROM SLOW EXTENSIONS.

(a) Critical Impact Velocity.

Material.	V_I from Direct Measurements.	V_I Extrapolated.
Cellulose acetate . .	> 250 sec. ⁻¹ 13° C. (initial temp.)	10 sec ⁻¹ 26° C.
Methyl methacrylate, 25 % D.B.P. . .	< 45 sec. ⁻¹ 12° C.	1 sec. ⁻¹ 26° C

(b) Work Absorption.

Material.	Work Absorption Found.	Ideal Total Work.
Cellulose acetate . .	130-160 Kg. cm./c.c.	120 Kg. cm./c.c.
Methyl methacrylate	260 Kg. cm./c.c. 14° C. 31.5 % D.B.P.	> 550 Kg. cm./c.c. 26° C., 28 % D.B.P.
Celluloid . . .	80-130 Kg. cm./c.c.	210 Kg. cm./c.c.

In addition, the material is broken at the centre with the consequent elimination of the edge variations, which normally cause irregular results in the breaking of celluloid. This test was carried out using a 0.336 Kg. bolt falling on a circular diaphragm of material 5.8 cm. in diameter and ~ 0.05 cm. thick.

Impact by Bolt Falling on Circular Lamina (15°-18° C.).—The bolt (0.336 Kg. unless otherwise stated) was allowed to drop on to the centre of the circle of material clamped at its edges.

Material.	Thickness.	Height just to crack.
Celluloid	0.0485 cm.	117-132 cm.
Cellulose acetate	0.051 cm.	93 cm.
Methyl methacrylate approx. 26 % D.B.P.	0.04-0.06 cm.	35-40 cm. (0.22 Kg.), 13-15 cm. (0.645 Kg.).

It will be noted that these tests give a low value for methacrylate and a high one for celluloid which, on this occasion, appears "stronger" than cellulose acetate.

Discussion.

(1) **The Limit of Extensibility.**—One of the more important properties of the non-ideal elastic extension is that of having a limit of extensibility characteristic of the material. The view that cellulose acetate had a limit of strain equal to 0·6 was put forward by Poole¹⁷ who carried out experiments on the deformation of a cellulose acetate gel in benzyl alcohol. On the other hand, rubber can show strains of the order of 7·8 and the methacrylate films described in this paper probably have a limit intermediate between these two figures. These variations can be logically explained on the assumption that they are connected with the flexibility of long molecular chains. Where the chain contains many single linkages able to rotate freely, the molecule tends to take up a strongly kinked configuration which is capable of a high degree of elongation. Where impeded rotation, or rings preventing all rotation, are present, the molecule is strung out in a linear configuration which cannot be so considerably elongated under stress. If this theory is correct, the same considerations should apply to solutions, and high values of the Staudinger constants for cellulose compounds should be obtained.

(2) **The Time Factor in Extension and Rupture.**—In the above experiments it has been shown that, if the conception of Critical Impact Velocity is added to that of a limit of extensibility and an Initial Cohesive Strength, then there exists the possibility of bringing the fast and slow deformations of plastic material into a single picture without obvious contradictions. In this way some of the difficulties associated with such conceptions as that of the "Tensile Product"¹⁸ may be overcome. On the other hand, apart from the extension limit, it has not, so far, proved possible to relate the properties of the tough plastics to the particular type of molecular chain. Instead, attention has been directed to the relation between the mechanical properties themselves, and in particular to the relation between deformation and destruction as recommended by Gurevich and Kobeko.¹⁹ The effects of temperature and variation in the quantity of plasticiser on extension have also been investigated, and the results are in general agreement with those of Alexandroff and Lazurkin.²⁰

An important outcome of these results is similar to that suggested by Kemp, Malm and Winspear²¹ who emphasized the need for studying stresses under varying types of service conditions. It would appear that there is no such property as a generalised impact strength. For instance, considering celluloid, cellulose acetate and plasticised methacrylates with 25-32% dibutyl phthalate, there are six mathematically possible permutations in which these materials may be placed. Three of them have been obtained in the very limited impact tests used in this paper, and there does not appear to be any conclusive reason why the other three should not be obtained in other tests. However, this is only an extreme case of the reversals of relative order with a change in the mode of testing, which have already been noted by Couzens.²¹ It follows that since more than one property may be measured in a given test, the test itself should be related to the properties and types of stressing which occur in use. In this connection further correlations between experience in testing and service of the type carried out by Burns and Wering²² may prove to be valuable.

In general, a greater knowledge appears desirable of the stresses and more particularly the times involved in various types of shock. It may

¹⁷ Poole, *Trans. Faraday Soc.*, 1925, 21, 19.

¹⁸ J. Behre, *Proc. Conf. Rubber Tech.*, London, 1938.

¹⁹ Gurevich and Kobeko, *J. Tech. Phys. U.S.S.R.*, 1940, 9, 1267.

²⁰ Alexandroff and Lazurkin, *Acta Physicochim. U.S.S.R.*, 1940, 12, 647.

²¹ Couzens, *J. Soc. Chem. Ind.*, 1940, 59, 209.

²² Burns and Wering, *A.S.T.M.*, 1938, 38, 39.

well transpire that these differ markedly in different cases, as for example, the falling of a moulded article, the impact of a moving object or the penetration of laminated glass, and that, in some cases, additional properties such as the specific gravity are involved. When an analysis of a particular type of shock condition is available, it should be possible to design one or more tests which will fully anticipate the conditions of service. In all probability it will be found that considerable empirical progress has already been made in this direction. At the same time it appears desirable to build up a knowledge of the behaviour of materials under the whole range of possible stresses so that the potentialities and limitations of any particular product may be fully understood.

Summary.

It is suggested in a theoretical discussion that the work taken up by any material under impact may be governed either by the rate at which deformation can take place or by the amount of possible deformation. The results of fast and slow extension experiments are examined and it is found that in this way apparent contradictions can be resolved.

Experiments are carried out on the extension and breaking of cellulose acetate film at different temperatures and it is concluded that temperature changes during adiabatic extension will not be so large as to alter fundamentally the character of the deformation.

The work absorption of different materials under changing conditions of testing varies both relatively and absolutely, and the validity of a generalised impact strength is questioned. A more precise formulation of shock conditions appears desirable.

I am indebted to Dr. R. F. Tuckett for much helpful advice in connection with the presentation of this work, and to Messrs. Colmore Adhesives Limited for permission to publish.

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KINETICS OF THE OXIDATION OF ORGANIC COMPOUNDS BY POTASSIUM PERMANGANATE. PART VI. BENZALDEHYDE.

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It has been shown previously^{1, 2} that permanganate may oxidise by two different processes, either (a) by the MnO_4^- ion directly reacting with the reducing agent, or (b) indirectly by the formation of the intermediate Mn^{III} ion. The latter mechanism is characterised by an initial induction period, but when the former is operative, the reaction is kinetically of the second order, the activation energy is less than in the latter process, and the reductant should possess a labile hydrogen atom. It was therefore anticipated that benzaldehyde would be oxidised by a bimolecular mechanism and that intermediate manganese ions would be ineffective. A previous study³ of the reaction of permanganate with benzaldehyde, acetaldehyde and formaldehyde in very dilute solution in presence of

¹ Alexander and Tompkins, *Trans. Faraday Soc.*, 1939, 35, 1156; *J. South African Chem. Inst.*, 1940, 23 (2), I.

² Mann and Tompkins, *Trans. Faraday Soc.*, 1941, 37, 201.

³ Seijee, *Anal. assoc. quím. Argentina*, 1923, II, 15; *A.C.S. Abstr.*, 1924, 18, 3517.

sulphuric acid, however, suggests that the process in each case is monomolecular. It is unfortunate that this paper is not here available since it appears to conflict with the work of Holluta⁴ who finds a second order reaction with formaldehyde in neutral solution. A re-examination of the oxidation of aldehydes is therefore necessary not only in view of these inconsistencies but also in obtaining further evidence in support of the theory previously put forward.¹

Experimental and Results.

The reaction of iodine with benzaldehyde was found to be sufficiently slow as to render any error negligible and there was little reaction in neutral solution between the manganese dioxide formed and the aldehyde. Consequently the iodometric method previously adopted has been used. Merck's benzaldehyde was used throughout after redistilling in an atmosphere of nitrogen. Known quantities were weighed by means of a pyknometer, transferred to a suitable volume of oxygen-free water and stored under nitrogen. The concentration was checked by using the method of Donnally⁵ which is accurate to 1%, even without correction for the dissociation of the aldehyde-bisulphite complex, and which thus formed a convenient method of confirming the purity of the aldehyde. The reaction proceeds in neutral solution according to the equation



since when a solution of the aldehyde of 0.0198 M. was allowed to react with a slight excess of KMnO_4 at 50° C. for 15 minutes and the excess oxidising agent estimated iodometrically, the strength of the solution was found to be 0.0195 M., after a correction had been applied for the subsequent slow oxidation of the benzoic acid formed. Because of the atmospheric oxidation of the aldehyde, particularly in presence of tri-manganic salts, the reaction mixture was maintained under nitrogen during any run.

A series, in which variable concentrations of benzaldehyde were used with a constant concentration (0.000766 M.) of KMnO_4 in neutral solution at $30.30 \pm 0.02^\circ\text{C}$.

is briefly summarised in Table I,

where initial velocities are given in terms of ml. N. thiosulphate per minute and the concentrations of aldehyde in ml. 0.0236 M. in a total volume of 250 ml.

ml. $\text{C}_6\text{H}_5\text{CHO}$.	Initial Rate.	Rate/ml. $\text{C}_6\text{H}_5\text{CHO}$.
10	0.189	0.0189
15	0.280	0.0187
30	0.576	0.0192
45	0.860	0.0191
60	1.18	0.0197

TABLE I

The rate of oxidation is thus directly proportional to the concentration of benzaldehyde. A similar series with constant aldehyde but variable permanganate concentrations shows that the reaction is also first order with respect to the oxidising agent, as has been found in all oxidations so far studied. The rate-determining process is thus probably due to bimolecular collisions between the aldehyde molecule and the permanganate ion. Some confirmation of this is afforded by the addition of Mn^{++} ions in the presence of sulphuric acid, which assists the formation of intermediate Mn^{++} (and Mn^{+++}) ions. A fall in the initial rate of oxidation which was approximately proportional to the Mn^{++} concentration due to the removal of MnO_4' ions¹ was found. The approximate nature of the results is due to the catalytic effect of the intermediate Mn ions on the

⁴ Holluta and Mutschin, *Z. physik. Chem. A*, 1930, 150, 381.

⁵ Donnally, *Ind. Eng. Chem. (Anal. Ed.)*, 1933, 5, 91.

Cannizzaro reaction, which occurs simultaneously. Similarly, the application of the familiar second-order expression, applied to one of the runs gives constant values for the velocity constants, k .

TABLE II

Time in Min.	ml. N. Thiosulph.	$1/t \cdot \log.(a-b-v)/b(a-v)$
2	0.0250	0.00230
4	0.0481	0.00228
6	0.0800	0.00230
8	0.0881	0.00230
10	0.106	0.00231
12	0.123	0.00235
14	0.141	0.00240
16	0.156	0.00242
20	0.183	0.00245
24	0.206	0.00247
30	0.231	0.00247

Temp. 30-30° C. 30 ml. 0.236 M. C_6H_5CHO ; 10 ml. 0.194 M. $KMnO_4$ in total volume of 250 ml.

removal by the Cannizzaro reaction, which depends on the square of the aldehyde concentration and which is promoted by the presence of oxidising agents.⁶ Consequently all velocity constants given here have been extrapolated to zero time. This value (k_0) at 30-30° C. is 20.4 l./g. mol./min. which is of the same order as that found in the formate oxidation (54.0 at 31.42° C. in the same units). The variation of k_0 with temperature is summarised in Table III. At the higher temperatures, the reaction mixture was quickly cooled to avoid errors due to the volatilisation of iodine during titration.

The Arrhenius equation is obeyed and the heat of activation is found to be 11,800 cal.

Since aldehydes normally show more pronounced reducing properties in alkaline solution, the influence of varying concentrations of NaOH has been

studied. The nature of the rate-determining process appears to be altered since the values of k , based on the second order equation, decrease rapidly with time, particularly at the higher pH values; k_0 , however, increases with increasing OH' ion concentration. This acceleration, whether calculated from the initial slopes of the oxidation curves or taking the k_0 values, is a linear function of the OH' ion concentration (if this is less than 0.15 N.) as shown in curve (a) of Fig. 1. Above this concentration a deep blue colour, largely masked by the permanganate colour, and a precipitation of manganese dioxide are apparent after a short period even in absence of the aldehyde, and in this region the increased rate is greater than corresponds to direct proportionality.

When the pH of the solution is decreased by the addition of acids the value of k_0 progressively increases while k now increases fairly rapidly

The slight increase in k with time is due to the simultaneous but slower oxidation of the benzoic acid produced; it is therefore more marked in solutions where there is a large excess of $KMnO_4$ present. When the aldehyde is in large excess, however, the constants fall with time due to its

TABLE III

Vel. Const. at Zero Time (g. mol./l./min.).	Temperature °C.
15.5	20.70
20.4	30.30
22.6	31.12
29.7	35.85
37.1	40.45
48.0	45.63

⁶ Kharasch, *J. Amer. Chem. Soc.*, 1935, 57, 1510.

with time, particularly at low pH . In Table IV is a summary of k_0 , at various values of pH , which was varied both by the addition of sulphuric acid and perchloric acid and measured by a glass electrode.

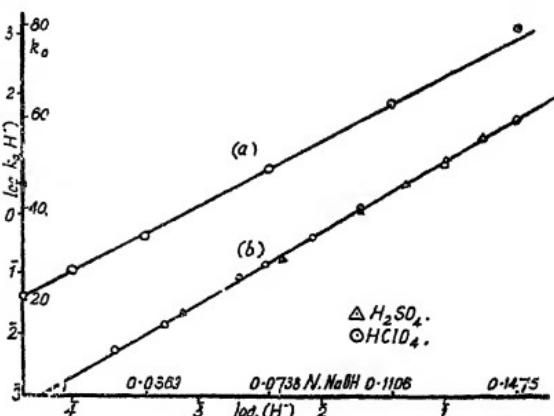
The conclusion is irrespective of the nature of the acid and, as shown in curve (b), Fig. 1, where for convenience $\log(H^+)$ is plotted against

$$\log(k_0 H^+),$$

the relation is well expressed by the equation

$$\log k_0 = 1.18 \log(H^+) + 2.26.$$

FIG. 1.



Discussion.

The oxidation of benzaldehyde by potassium permanganate in neutral solution follows the second order equation. The subsequent oxidation

of the benzoic acid produced, which has a rate constant of only 1.97×10^{-4} l./g. mol./sec. at $25^\circ C.$ ⁶ as compared with 3.40×10^{-1} at $30.30^\circ C.$ for benzaldehyde, is negligible in the initial stages of the reaction but becomes important as the reaction proceeds, particularly when a large excess of permanganate is present. The bimolecular character is confirmation of the theory proposed previously since it is clear that the polar effect of the

TABLE IV

pH Values.		k_0 Values.	
HClO ₄	H ₂ SO ₄	HClO ₄	H ₂ SO ₄
4.10	4.10	19.1	19.0
—	3.65	—	26.2
—	3.27	—	27.5
3.11	—	30.9	—
—	2.67	—	36.8
2.30	—	37.1	—
—	2.27	—	40.0
—	2.07	—	49.4
—	1.07	—	55.0
1.28	—	64.5	—
—	1.00	—	67.9
0.98	—	72.0	—
—	0.69	—	80.9
0.68	—	80.3	—
0.41	—	93.6	—
—	0.40	—	94.8

phenyl group and of the carbonyl group will combine to weaken the C—H link. The oxidation likewise proceeds with the lower activation energy of 11,800 cal. and is to be compared with those obtained in the

⁷ Weiss, *Trans. Faraday Soc.*, 1941, 37, 782.

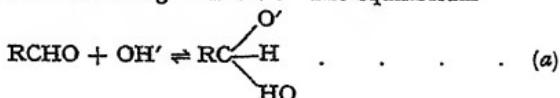
⁸ Hinshelwood, *J.C.S.*, 1936, 368.

other bimolecular oxidations with permanganate, *viz.*, formic acid (12,100),^{1,2} benzoic acid (12,700),³ and picric acid (12,200).^{4,5,6} The closeness of these values suggests that the rate-determining process in all these oxidations is of the same general type. The application of molecular statistics to the formate oxidation gave good agreement between the experimental and calculated rates when the usual expression

$$k_0 = N_0/1000 \cdot \sigma_{11} \cdot (8\pi RT(M_1 + M_2)^{1/2}) \cdot e^{-E/RT},$$

was employed. In the present reaction, using as before a value of 5^{1/2} A. for σ_{11} , the calculated rate at 30–30° C. is 2.49 l./g. mol./sec. as compared with the experimental one of 0.34 in the same units. The agreement is good in view of the uncertainty in the value of σ_{11} and of the probability of there being necessary a specific orientation in collision because one reactant is a fairly large and asymmetric molecule. Such orientation, if present, would be much smaller in the case of the formate ion. It is clear that solvent molecules do not enter into ternary collision with the solute molecules as has been suggested in oxidation of the picric acid.¹⁰ The values of k_0 have been shown to increase linearly with OH' concentration if this is less than 0.15 N. This effect may be due to the production of the manganate ion which oxidises the aldehyde at a faster rate than does permanganate. The amount of the former in solution can be calculated from the e.m.f. data of Sackur and Targener¹² when an equilibrium constant $K = \frac{(MnO_4')^2(OH')^4}{(MnO_4'')^3} = 53.1$ is obtained. Departure from linearity

(Fig. 1) is found between 0.15 and 0.30 N. alkali when $\frac{(MnO_4')^2}{(MnO_4'')^3} = 330$ and 81 respectively. Below 0.15 N. the linear increase is therefore not due to manganate formation, but the additional acceleratory effect at higher pH may be accounted for by the production of this ion. This is supported by the darkening of the permanganate colour caused by the appearance of the green manganate, which, as expected in dilute alkaline solution, subsequently decomposes to form a precipitate of MnO₂, even in absence of the aldehyde. The transient presence of the bright blue mangani-manganate¹³ is unlikely since this is normally not obtained in alkalies of strength less than 4 N.¹⁴ Moreover, Holluta¹⁵ finds that this complex causes a retardation, and not an acceleration, in the HCHO/manganate reaction because its stability is increased by increasing pH. According to work of Conant¹⁶ the acceleration of the oxidation of aldehydes by dilute alkalies is a general feature and not dependent on the nature of the oxidising agent. It is therefore believed to be due to the formation of the "aldehydiate" ion, which is oxidised more rapidly than the C₆H₅CHO molecule. Holluta,¹⁵ however, advanced the same theory to explain a retardation caused at higher OH' ion concentration in the HCHO/manganato reaction. He assumed the production of the H₃C(OH)⁻O' ion which, he suggested, was oxidised more slowly than the HCHO molecule. This, however, is not in keeping with the fact that aldehydes in general show quite definite reducing properties in alkaline solution, whereas the molecule has more of an oxidising character. The equilibrium



¹ Hill and Tompkins, *in the press*.

² Mochlyn-Hughes and Musgrave, *Trans. Faraday Soc.*, 1933, 29, 1162.

³ Hinshelwood, *J.C.S.*, 1936, 368.

⁴ Sackur and Targener, *Z. Elektrochemie*, 1915, 18, 1718.

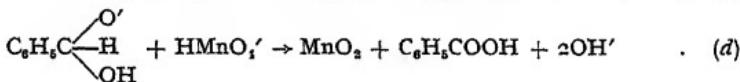
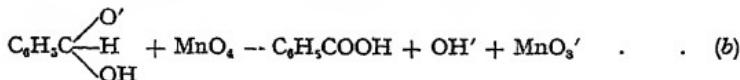
⁵ Holluta, *Z. physik. Chem.*, 1923, 106, 324.

⁶ Auger and Billy, *Compt. rend.*, 1904, 138, 500.

¹² Holluta, *Z. physik. Chem.*, 1923, 106, 324; 107, 249, 333.

¹⁶ Conant, *J. Amer. Chem. Soc.*, 1930, 52, 409.

has been frequently assumed on previous occasions, and there is a certain amount of direct experimental evidence for it.¹⁷ The equilibrium (*a*) accounts for the linear increase of k_0 with increasing OH' ion concentration, if we assume that the oxidation of the ion proceeds with a smaller activation energy than that of the molecule. This seems probable because there will be a high electron density at the singly bonded oxygen atom of the ion; this weakens the C—H link by a mesomeric effect and thus makes an attack by an electrophilic reagent, such as the MnO₄' ion, energetically easier. Similar reasoning applied to the HCOOH/MnO₄ reaction will account for the more rapid oxidation of the formate ion as compared with the HCOOH molecule. The subsequent course of the oxidation would follow the same course as in the formate ion oxidation, *i.e.*

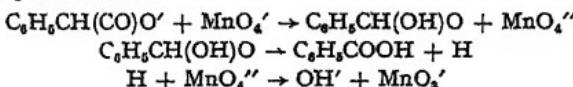


where the reaction (*b*) is rate-determining. Thus the overall rate would be

$$k_0 = (\text{MnO}_4')(\text{C}_6\text{H}_5\text{CHO})(\text{OH}')$$

as found experimentally.

Another mechanism is suggested by the work of Loew, Müller and others. Loew¹⁸ has shown that when HCHO is treated with Ag₂O or Cu₂O in alkaline solution, formic acid and hydrogen are formed and the amount of acid produced is in excess of that corresponding to the oxygen in the oxides. CuO, K₂Fe(CN)₄, K₂S₂O₈,¹⁹ and H₂O₂²⁰ react similarly. Furthermore, Müller²¹ obtained one molecule of acid and one equivalent of hydrogen for each farad in the anodic oxidation of C₆H₅CHO and CH₃CHO in alkaline solution with Ag or Cu anodes. Molecular hydrogen is mainly formed in these experiments if the oxidising agent is present in excess. In the present work no evolution of hydrogen has been detected, nor is there any large discrepancy in the amount of oxidising agent used to the amount of aldehyde oxidised—this, however, need not exclude the following mechanism



and the MnO₃' ion reacting as previously. By analogy with the formate ion oxidation, where the activation energy differs only by 300 cal. and where no hydrogen formation is found, the former mechanism appears more probable.

According to the equation $k_0 = (\text{MnO}_4')(\text{C}_6\text{H}_5\text{CHO})(\text{OH}')$ the value of k should increase as the oxidation proceeds because of the production of OH' ions. The reaction is, however, complicated by the oxidation of "aldehydate" ion by the aldehyde molecule (Cannizzaro reaction). The aldehyde concentration used in the bimolecular expression is deduced from the loss of oxidising power of the KMnO₄ and will thus be in excess of that actually present. The calculated k value must necessarily fall.

¹⁷ Hérold, *Z. physik. Chem. B*, 1923, 18, 266.

¹⁸ Loew, *Ber.*, 1887, 20, 144.

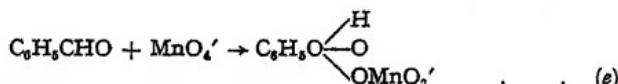
¹⁹ Müller, *Ann. Chem.*, 1920, 420, 241.

²⁰ Geisow, *Ber.*, 1904, 37, 515.

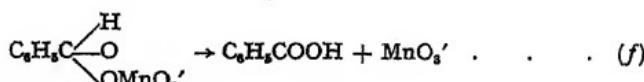
²¹ Lyford, *J. Amer. Chem. Soc.*, 1907, 29, 1227.

This should be most evident at high pH and with excess aldehyde since the Cannizzaro reaction is kinetically of the third order,²² i.e. its rate = $k \cdot (\text{C}_6\text{H}_5\text{CHO})^2 \cdot (\text{OH}')$. An attempt has been made at an approximate correction and such a correction does give a much less rapid decrease of k . Experimental confirmation, however, is not easy because of the difficulty of analysis of organic substances in presence of inorganic compounds, and because the velocity constants used are too small due to the catalytic effect of oxidising agents²³ on the Cannizzaro reaction.

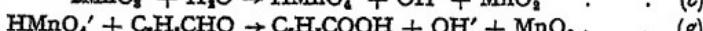
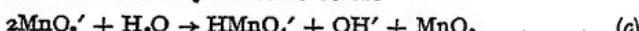
The effect of the addition of acids in increasing k_0 is shown to be due solely to the effect of the hydrogen ion and not to the undissociated molecule, or its anion as in the acid catalysis of acetal formation,²⁴ since it is independent of whether perchloric acid (which forms no complex) or sulphuric acid (which forms the complex $\text{Mn}(\text{SO}_4)_2 \cdot 2\text{H}_2\text{O}'$ ^{25, 26}) is used. The formation of the enolic form is unlikely since the aldol condensation is not found with benzaldehyde and also the oxidation is still very rapid in 2 M. sulphuric acid, where the amount of the enolic form must be minute. Moreover, no simple relationship exists between k_0 and the pH as would be expected by this theory. Similar results to those recorded here have been obtained in the oxidation of the formate ion by permanganate in alkaline solution by Holluta,²⁷ who suggests that there must exist some relation between "the oxidising power and oxidation potential on the one hand and the velocity of the reaction on the other." This possibility has been studied in some detail by Conant *et alia*^{16, 28} who showed that the speed of certain irreversible oxidation was a function of the apparent oxidation potential (A.O.P.) of the oxidising agent. Permanganate, however, was not studied, since with aldehydes the reaction "was too rapid and had peculiarities of its own." In this theory it is necessary that the primary step should involve two equivalents of the oxidising agent and that the rate should be monomolecular with respect to the oxidising agents, as is found here. In such circumstances the predominant factor in determining the rate is the A.O.P. of the oxidising agent. It must be emphasised, however, that there is no reason to suppose that the rate will always be some function of the potential since some specific property of the reagent may be more important. Thus the effect is not found in alkaline solution where the aldehyde ion is the reducing agent nor in the oxidation of the formate ion in acid solution.¹ It follows that there must be a reversible step (e) which precedes a slow (rate determining) irreversible reaction (f). Thus in the present reaction, this would be



followed by the breakdown of the complex



The subsequent fate of the MnO_3' ion is as before



²² Birstein and Lebanow, *Z. anorg. Chem.*, 1927, 160, 377.

²³ Unpublished expts. of Weiss, ⁷; *v. also* ⁶.

²⁴ Adkins *et alia*, *J. Amer. Chem. Soc.*, 1922, 44, 2749; 1923, 45, 1552.

²⁵ Ubbelohde, *J.C.S.*, 1935, 1605.

²⁶ Tompkins, *Trans. Faraday Soc.*, 1942, 38, 131.

²⁷ Holluta and Mutschin, *Z. physik. Chem. A*, 1930, 150, 381.

²⁸ Conant *et alia*, *J. Amer. Chem. Soc.*, 1930, 52, 409; 1928, 50, 2783; 1926, 48, 3178, 3220.

The formation of such a complex is similar to that suggested by Weiss⁷ as the first step in the benzoin synthesis, and the mechanism is essentially the same as that previously proposed for the oxidation both of the "aldehydate" and of the formate ion. The effect of the decrease of p_H will be to increase the amount of the complex in (e), (thereby leading to a faster rate in the irreversible step (f)), since increasing acidity will cause a rise in the A.O.P. of the permanganate. Conant has given linear plots relating the A.O.P. and the hydrogen ion concentration, and the slope of these was found to be independent of the nature of the oxidising agent. Using his fundamental equation for aldehydes

$$E = E_0 + 0.003T \log .0.01/k_0$$

where E is the A.O.P., and E_0 the normal oxidation-reduction potential of the oxidising agent, and the average slope of his experimental $\log (H^+)/E$ plots, which for acetaldehyde and formaldehyde is -10 and for *n*- and *iso*-butyraldehyde is -7.8, we obtain the equation

$$0.003T \log K_0 = 0.112 \log (H^+) + \text{const.}$$

The slope of curve (b) in Fig. 1 here should thus be $\frac{0.112}{0.003T} = 1.23$

at 30° C., i.e. 303° A. whereas the experimental value is 1.18. The agreement is better than can be expected since an error of 5 mv. in the e.m.f. method of Conant would lead to an error of 20 % in the value of k_0 . It can be anticipated that a similar value would be found in the oxidation of other aldehydes by KMnO₄, since there is no reason to suppose, from Conant's results, that their specific properties will be more important than the A.O.P. in the determining rate.

Work is being continued along these lines with other aldehydes.

Summary.

The kinetics of the oxidation of benzaldehyde by potassium permanganate has been investigated. In neutral solution it is kinetically of the second order, with a velocity constant of 0.34 l./g. mol./sec. at 30-30° C. and an activation energy of 11,800 cal. in the temperature range 26.70-45.63° C. In alkaline solution the bimolecular rate constant (k) falls with time, but the extrapolated values for zero time (k_0) increase linearly with the OH⁻ concentration up to 0.15 N., when an additional acceleratory effect due to manganese formation is observed. The hydroxyl ion reacts with the aldehyde to form the "aldehydate ion" which is more rapidly oxidised than the molecule. In acid solution, k increases with time and k_0 depends solely on the H⁺ ion concentration according to the equation

$$\log k_0 = 1.18 \log (H^+) + 2.26.$$

This is interpreted in terms of the theory of apparent oxidation potential of Conant. This potential is related to the rate, and good quantitative agreement is obtained between values found here and those which can be calculated from his experimental results. Mechanisms similar to that suggested in the formate ion oxidation are found to be applicable and the theory previously proposed in this series has been confirmed.

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ARRANGEMENT OF DOUBLE MOLECULES ON A LATTICE.

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The number of ways $g(N, \frac{1}{2}N\theta)$ of arranging $\frac{1}{2}N\theta$ double particles on a lattice of N points with each particle occupying two adjacent points was first investigated by Fowler and Rushbrooke,¹ who succeeded in getting the number for $\theta \sim 0, 1$. Soon after their work, one of us obtained an approximate formula² valid for all values of θ by studying the adsorption of double molecules upon a solid surface, calculating the equilibrium conditions by a method due to Bethe and Peierls³ and deducing therefrom the desired number. The result is

$$N^{-1} \log g(N, \frac{1}{2}N\theta) = - (\frac{1}{2}z - \theta) \log z + \frac{1}{2}(z - \theta) \log(z - \theta) - \frac{1}{2}\theta \log \theta - (1 - \theta) \log(1 - \theta), \quad (1)$$

where z is a number belonging to the lattice denoting the number of nearest neighbours surrounding a site. The validity of this approximate formula has never been questioned and its investigation is the purpose of the present paper.

Our investigation falls into two parts. Firstly, since the validity of Bethe's method depends upon how quickly the results obtained by using higher and higher approximations converge, we calculate the equilibrium properties of the said adsorption problem by employing Bethe's second approximation instead of the first approximation as was employed in ref.² and compare the corresponding results. If the results for $g(N, \frac{1}{2}N\theta)$ obtained in the two approximations are nearly the same, it will be safe to assume that they are not far from the actual $g(N, \frac{1}{2}N\theta)$. In the following calculations of the equilibrium properties of the adsorption problem, we restrict ourselves to cases where the sites of accommodation lie on a lattice of simple cubic system (§ 1), and on a (1, 0, 0) section of

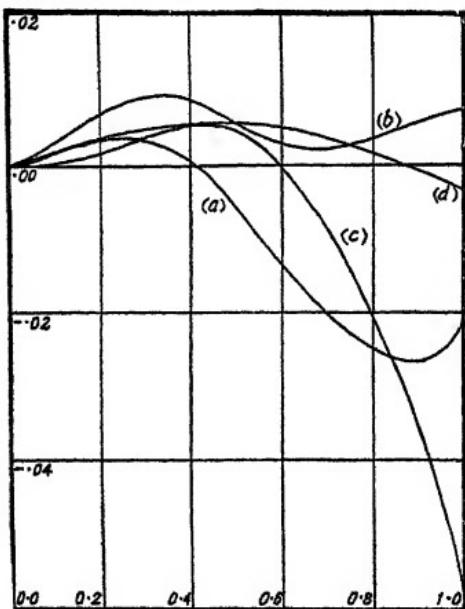


FIG. I.

- Curve (a) $\log(\lambda_1/\lambda_0)$ against θ , $z = 6$,
- (b) $\log(\lambda_2/\lambda_0)$ against θ , $z = 6$,
- (c) $\log(\lambda_1/\lambda_0)$ against θ , $z = 4$,
- (d) $\log(\lambda_2/\lambda_0)$ against θ , $z = 4$.

¹ Fowler and Rushbrooke, *Trans. Faraday Soc.*, 1937, 33, 1272.

² Chang, *Proc. Roy. Soc. A*, 1939, 169, 512.

³ Peierls, *Proc. Camb. Phil. Soc.*, 1936, 32, 471.

the same lattice (§ 2), with z taking therefore the value 6 for the first case and the value 4 for the second. The results turn out to be nearly the same as those given by the first approximation.

Secondly, we may calculate $g(N, \frac{1}{2}N\theta)$ rigorously for a few simple cases following a method developed by one of us,¹ and see for such cases the extent to which $g(N, \frac{1}{2}N\theta)$ as given by (1) agrees with the actual

$$g(N, \frac{1}{2}N\theta).$$

The method enables us to calculate the asymptotic value of $g(N, \frac{1}{2}N\theta)$ and similar numbers as N approaches infinity, provided that the N points lie on a number of parallel planes containing in each a small number of points. Here we consider the special case in which the N points are on two horizontal straight lines with points on the one lying on the top of those on the other. The agreement between $N^{-1} \log (N, \frac{1}{2}N\theta)$ obtained this way and the right-hand side of (1) is also satisfactory.

1. Adsorption of Double Molecules for $z = 6$.

As always in the application of Bethe's method, we introduce a typical aggregate of sites. Let our chosen typical aggregate be a group of 25 sites, with one site in the centre and two shells of neighbours surrounding it, the first shell containing 6 sites and the second 18. Let n_0 be 1 or 0 according as the central site is occupied or not and let n be the number of occupied sites in the first shell. The grand partition function for configurations with the numbers n_0 and n is*

$$1(n_0, n) \lambda^{2n} (1 + \lambda \zeta)^{18-n+n_0}, \dots \quad (2)$$

where $f(n_0, n)$ is, for a given n_0 and n , the number of ways of arranging the molecules inside the aggregate, after ignoring altogether the presence of molecules whose one end or both ends are outside the aggregate, and the symbols λ and ζ have their meanings given in ref.². Formula (2) can be easily understood if we remember that $18 - n + n_0$ is the number of sites in the second shell which are either unoccupied or occupied by molecules which are partly outside the aggregate. (This statement requires the assumption that sites in the first shell do not form nearest

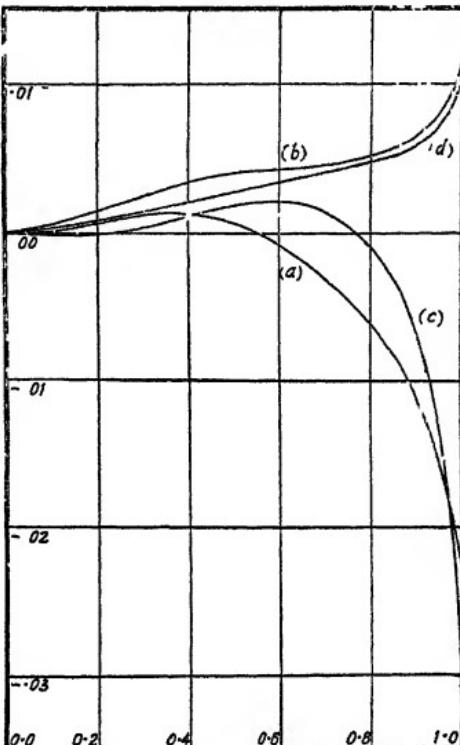


FIG. 2.

- Curve (a) $N^{-1} \log (g_1/g_0)$ against θ , $z = 6$,
 (b) $N^{-1} \log (g_2/g_0)$ against θ , $z = 6$,
 (c) $N^{-1} \log (g_1/g_0)$ against θ , $z = 4$,
 (d) $N^{-1} \log (g_2/g_0)$ against θ , $z = 4$.

¹ Chang and Ho, *Proc. Roy. Soc., A*, 1942, 180, 345.

* Interactions between adsorbed molecules are assumed to be zero.

neighbours, which is evidently satisfied in the present case.) Writing ϵ for $\lambda\xi$ and $F(n_0, n)$ for (2) we obtain as the equations for determining the fraction of adsorption θ in terms of λ

$$\begin{aligned} \theta \sum_{n_0, n} F(n_0, n) &= \sum_{n_0, n} n_0 F(n_0, n) = \frac{1}{6} \sum_{n_0, n} n F(n_0, n) \\ &= \frac{1}{18} \sum_{n_0, n} (n - n_0 + \epsilon \frac{\partial}{\partial \epsilon}) F(n_0, n), \quad . . . \quad (3) \end{aligned}$$

which expresses the fact that the probability of occupation is the same for all sites. Hence it remains to obtain $f(n_0, n)$ by direct enumeration and solve for θ . The numbers $f(n_0, n)$ are shown in Table I. With these numbers known, equations (3) can be solved.

TABLE I.

(n_0, n) .	$f.$	(n_0, n) .	$f.$	(n_0, n) .	$f.$
(0, 0)	1	(0, 5)	12,282	(1, 4)	6,852
(0, 1)	30	(0, 6)	8,875	(1, 5)	15,258
(0, 2)	363	(1, 1)	6	(1, 6)	13,026
(0, 3)	2,092	(1, 2)	150		
(0, 4)	7,629	(1, 3)	1,380		

Equations (3) give in fact two relations between λ and θ . Ignoring the last equality, we obtain a solution $\lambda = \lambda_1(\theta)$, and equating $\theta \sum F(n_0, n)$ to $\sum n F/6$ and $\sum (n - n_0 + \epsilon(\partial/\partial \epsilon))F/18$ we get another solution $\lambda = \lambda_2(\theta)$. The relation between λ and θ as given by the first approximation is

$$\lambda = (z - \theta)^{\frac{1}{2}} \theta^{\frac{1}{2}} / z(z - \theta). \quad \quad (4)$$

Let us denote the right-hand side of the above equation by $\lambda_0(\theta)$ and plot $\log \lambda_1/\lambda_0$ and $\log \lambda_2/\lambda_0$ against θ . The curves are shown in Fig. 1 together with corresponding curves for $z = 4$, and there we see that the differences between λ_1 , λ_2 and λ_0 are small.

The number $g(N, \frac{1}{2}N\theta)$ can be obtained as usual from the formula

$$\frac{1}{N} \log g(N, \frac{1}{2}N\theta) = - \int_0^\theta \log \lambda(\theta) d\theta, \quad \quad (5)$$

and hence from $\lambda_1(\theta)$ and $\lambda_2(\theta)$ we get two values for $g(N, \frac{1}{2}N\theta)$, say $g_1(N, \frac{1}{2}N\theta)$ and $g_2(N, \frac{1}{2}N\theta)$. Curves expressing the variation with θ of $\log g_1/g_0$ and $\log g_2/g_0$, where $N^{-1} \log g_0$ is given by the right-hand side of (1), are given in Fig. 2, together with corresponding curves for $z = 4$.

2. Adsorption of Double Molecules for $z = 4$.

The calculations and formulae involved are exactly the same as those in the preceding section except that the number 18 in (2) is now replaced

TABLE II.

(n_0, n) .	$f.$	(n_0, n) .	$f.$	(n_0, n) .	$f.$
(0, 0)	1	(0, 3)	84	(1, 2)	36
(0, 1)	12	(0, 4)	47	(1, 3)	100
(0, 2)	50	(1, 1)	4	(1, 4)	84

by 8, numbers 6 and 18 in (3) by 4 and 8 respectively, and the numbers $f(n_0, n)$ take the values shown in Table II. The results are given in Figs. 1 and 2.

3. Rigorous Value of $g(N, \frac{1}{2}N\theta)$ for $z = 3$.

In this section, we endeavour to find $g(N, \frac{1}{2}N\theta)$ rigorously for the case in which the N points lie on two horizontal straight lines, with the points on one of them lying on the top of those of the other.

In ref.⁴ it is proved that if in a certain arrangement of g kinds of particles A, B, . . . on a straight line, we let n_A, n_B, \dots denote the numbers of A, B, . . . particles, $X_{AA}, X_{AB}, \dots, X_{BA}, X_{BB}, \dots$ denote the numbers of pairs of neighbours of the type AA, AB, . . . , BA, BB, . . . , the function $\Psi^{(q)}(\xi, \lambda_A, \lambda_B, \dots, \eta_{AA}, \eta_{AB}, \dots)$, which is defined to be the summation of

$$(\xi \lambda_A)^{n_A} (\xi \lambda_B)^{n_B} \dots \frac{X_{AA}}{\eta_{AA}} \frac{X_{AB}}{\eta_{AB}} \dots \frac{X_{BA}}{\eta_{BA}} \frac{X_{BB}}{\eta_{BB}} \dots \dots \quad (6)$$

over all such arrangements with no restrictions regarding the values of the n 's and the X 's, is a rational function of ξ , λ 's and η 's, whose denominator is the determinant

$$\begin{vmatrix} 1 - \xi \lambda_A \eta_{AA} & -\xi \lambda_B \eta_{AB} & \dots & -\xi \lambda_Q \eta_{AQ} \\ -\xi \lambda_A \eta_{BA} & 1 - \xi \lambda_B \eta_{BB} & \dots & -\xi \lambda_Q \eta_{BQ} \\ \vdots & \vdots & \ddots & \vdots \\ \vdots & \vdots & \ddots & \vdots \\ -\xi \lambda_A \eta_{QA} & -\xi \lambda_B \eta_{QB} & \dots & 1 - \xi \lambda_Q \eta_{QQ} \end{vmatrix} \quad (7)$$

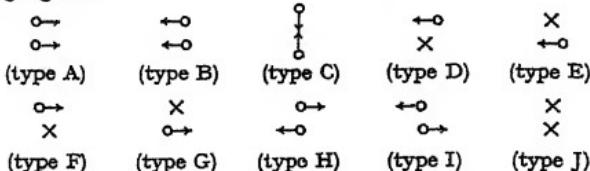
Now if, in a certain arrangement of a number of double particles on two rows of points, we let N denote the total number of points, n the number of double particles and X the number of pairs of neighbours formed by points occupied by two different particles, and if we let $\Phi(\xi, \lambda, \eta)$ to be a function of ξ , λ and η defined as the summation of

$$\xi^N \lambda^n \eta^X$$

over all such arrangements with no restrictions regarding the values of N , n and X , it is obvious from Cauchy's theorem that the number of ways of arrangements corresponding to a given N , n and X , say $g(N, n, X)$, is

$$\frac{1}{(2\pi i)^3} \oint \oint \oint \frac{d\xi d\lambda d\eta}{\xi^{N+1} \lambda^{n+1} \eta^{X+1}} \Phi(\xi, \lambda, \eta) \quad \dots \quad \dots \quad \dots \quad (8)$$

with an obvious meaning for the path of integration. On the other hand, introducing figures



where "x" represents an unoccupied point and "o" with an arrow an occupied point with the arrow pointing to the direction of that neighbour occupied by the same double particle, we see at once that $\Phi(\xi, \lambda, \eta)$ is nothing but the summation of

$$\begin{aligned} & \xi^{n_A + n_B + \dots + n_J} \lambda^{n_A + n_B + n_C + \frac{1}{2}(n_D + n_E + n_F + n_G)} \\ & \times \lambda^{n_H + n_I} \eta^{n(X_{BA} + X_{BC} + X_{CA} + X_{CC}) + X_{BF} + X_{BG} + X_{CG} + X_{CH}} \\ & \times \eta^{X_{DA} + X_{DC} + X_{DF} + X_{EA} + X_{EC} + X_{EG} + X_{EH} + X_{IH}} \\ & \times O(X_{AA} + X_{AC} + X_{AD} + \dots) + (X_{BB} + X_{BD} + \dots) + \dots + (X_{JB} + \dots + X_{JI}) \quad \dots \quad (9) \end{aligned}$$

over various arrangements of ten kinds of figures on a straight line, with no restriction over the values of n and X , and hence can be obtained from $\Psi^{(10)}$ (ξ , λ 's, η 's) by performing a suitable replacement of the variables. Our task is therefore to obtain $\Phi(\xi, \lambda, \eta)$ in this way and perform the integration in (8). The denominator of Φ is in fact

$$-\lambda^{-s} \eta^{-s} [\lambda \eta^s (1 + a\eta) + a^s (1 - \eta)(1 - a + a\eta)] [-\lambda^2 \eta^4 (a\eta - 1)(a^2 \eta^2 + a\eta - 1) \\ + \lambda a \eta^3 (1 + a) + \lambda a^2 \eta^2 (1 - \eta)(2(1 + \eta) + a(1 + 2\eta) + a^2 \eta (1 - \eta - \eta^2) \\ + a^3 \eta^2 (1 - \eta)) + a^3 (1 - \eta)(1 + a - a\eta)\{\eta - a(1 - \eta)^2 (1 + a\eta)\}], \quad (10)$$

a being short for $\xi^2 \lambda \eta$, and the numerator will not be given since it does not affect $\log g(N, n, X)$ if we do not want terms of the order unity in its expression (ref.⁴).

From the definition of $\Phi(\xi, \lambda, \eta)$ it follows

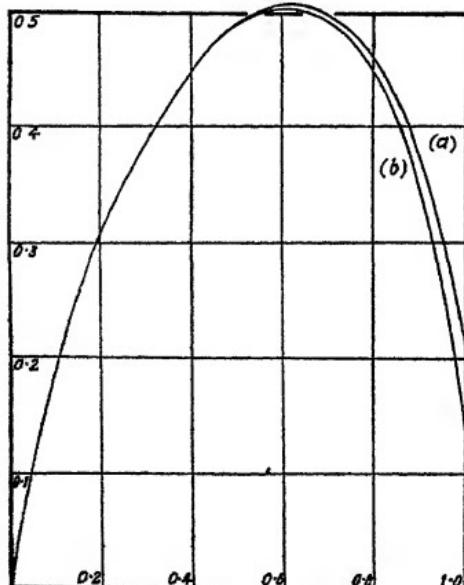
$$g(N, \frac{1}{2}N\theta) = \frac{1}{(2\pi^2)^2} \oint \oint \frac{d\xi d\lambda}{\xi^{N+1} \lambda^{N\theta+1}} \Phi(\xi, \lambda, 1). \quad . \quad . \quad . \quad (11)$$

The integration can be carried out as follows. First we transform the variables ξ and λ to b and λ where $b = \xi^2 \lambda$; next we integrate with respect to λ in the usual manner; and finally we integrate with respect to b by using the method of steepest descent due to Fowler⁵ (ref.⁴), after seeing that all the conditions for the applicability of the method are satisfied. In this way we get

$$N^{-1} \log g(N, \frac{1}{2}N\theta) = \frac{1}{2}(1 - \theta) \log \frac{b(1 + b)}{(1 - b)(1 - b - b^2)} - \frac{1}{2} \log b, \quad (12)$$

where b is the only positive root of the equation

$$1 - \theta = \frac{1}{1 - b^2} + \frac{1}{1 - b - b^2}. \quad . \quad . \quad . \quad (13)$$



$N^{-1} \log g$ obtained in this way, and according to (1) with s put as 3, are plotted against θ in Fig. 3. It can be seen that the agreement is good, particularly for small θ .

No. (8) can be integrated in a similar manner. First

FIG. 3.

$N^{-1} \log g$ against θ for $s = 3$, Curve (a) according to (12) and (13), (b) according to (1).

we transform the variables ξ , λ and η to a , λ and η where $a = \xi^2 \lambda \eta$; next we split $\Phi(a, \lambda, \eta)$ into partial fractions

$$\sum_{i=1,2} \frac{c_i(a, \eta)}{\lambda - \lambda_i(a, \eta)}$$

plus a polynominal in λ , and integrate with respect to λ in the usual manner; and finally apply the

⁴ Fowler, *Statistical Mechanics*, 1937.

method of steepest descent for the integration to a and η . Since apart from the factor $a^{-(\frac{1}{2}N+1)}\eta^{-(X-\frac{1}{2}N+1)}$, the integrand in the last integration is merely the coefficient of $\lambda^n \cdot \frac{1}{2}N$ in $\Phi(a, \lambda, \eta)$ which is essentially a series in a , λ and η with positive coefficients, it must be a series in a and η with positive coefficients. The first part in Fowler's proof for his theorem on the method of steepest descent can be taken over here with the result that the integrand in the last integration has one and only one minimum, say at a_s, η_s , on the positive real axes of a and η inside the domain of its convergence. The integrand is

$$\{\Sigma c_i(a, \eta)[\lambda_i(a, \eta)]^{\frac{1}{2}N-n} a^{-(\frac{1}{2}N+1)}\eta^{-(X-\frac{1}{2}N+1)}\}. . . . (14)$$

Since the two terms within the brackets in (14) are both raised to a power $\frac{1}{2}N - n$ which is a very large number, one of them will be negligibly small compared with the other. Neglecting the presence of the smaller term in the neighbourhood of a_s and η_s , we have the integrand in the form

$$c(a, \eta)\lambda(a, \eta)^{\frac{1}{2}N-n} a^{-(\frac{1}{2}N+1)}\eta^{-(X-\frac{1}{2}N+1)},$$

which shows plainly that the minimum cannot but be a sharp one (with second derivatives with respect to a and η of the order N or n), so that we can apply the method of steepest descent as usual.

The result is as follows. For $\frac{1}{2}N > n$, let us find a and η which satisfies $\lambda_1 > \lambda_2$ and

$$\frac{\partial}{\partial a}\{\dots\} = \frac{\partial}{\partial \eta}\{(\frac{1}{2}N-n)\log \lambda_1(a, \eta) - \frac{1}{2}N \log a - (X - \frac{1}{2}N) \log \eta\} = 0, \quad (15)$$

or which satisfies $\lambda_1 < \lambda_2$ and (15) with λ_1 replaced by λ_2 . For $\frac{1}{2}N < n$, let us find a and η which satisfies $\lambda_1 < \lambda_2$ and (15) or which satisfies $\lambda_1 < \lambda_2$ and (15) with λ_1 replaced by λ_2 . The existence of such a and η is ensured by the preceding discussions. Substitution into

$$-\frac{1}{2}N \log a - (X - \frac{1}{2}N) \log \eta + \text{Max}[(\frac{1}{2}N-n)\log \lambda_1, (\frac{1}{2}N-n)\log \lambda_2] \quad (16)$$

gives us the required $\log g(N, n, X)$.

An approximate formula for $N^{-1} \log g(N, \frac{1}{2}N\theta, X)$ deduced in an analogous manner to that of deducing (1) is^{*}

$$\begin{aligned} & \frac{1}{2}z \log z - (z-1)\theta \log z + \frac{1}{2}(2z-3)\theta \log z \\ & + \theta(z-1) \log(z-1) + (z-1)(1-\theta) \log(1-\theta) + \frac{1}{2}(2z-3)\theta \log \frac{1}{2}\theta \\ & - (X/N) \log(2X/N) - [(z-1)\theta - 2X/N] \log[(z-1)\theta - 2X/N] \\ & - \frac{1}{2}[z - (2z-1)\theta + 2X/N] \log[z - (2z-1)\theta + 2X/N]. . . . (17) \end{aligned}$$

TABLE III.

$\theta = 0.30$.		$\theta = 0.50$.		$\theta = 0.90$.	
X/N .	$\log g$ from (16).	$\log g$ from (17).	X/N .	$\log g$ from (16).	$\log g$ from (17).
0.0000	0.1591	0.1580	0.000	-0.1087	0.750
0.00358	0.1707	0.1659	0.100	0.1261	0.759
0.0253	0.1873	0.1859	0.182	0.1953	0.2111
0.0667	—	0.1967	0.230	0.2344	0.2383
		(m)			0.7714
0.0712	0.1970	0.1966	0.300	—	0.2526
	(m)				(m)
0.149	0.1749	0.1655	0.3067	0.2535	0.2525
				(m)	(m)
0.248	0.1034	0.0360	0.435	0.2196	0.1979
0.300	0.0314	-0.1139	0.545	0.1390	0.0510
			0.600	0.0627	-0.1087

((m) denotes the maximum point.)

* Chang, Proc. Camb. Phil. Soc., 1939, 35, 265.

$N^{-1} \log g(N, \frac{1}{2}N\theta, X)$ obtained here for two rows of points, i.e. from (16), will be given below for a few values of θ and X/N , and for comparison, values for the same θ and X/N according to (17) with z put as 3 will also be given (Table III).

It may be pointed out that the allowable range of (X/N) for $\theta = 0.30$ is according to both the present method and (17) from 0 to 0.03, that for $\theta = 0.9$ from 0.75 to 0.9, while the allowable range of X/N for $\theta = 0.60$ is according to the present method from 0.1 to 0.6 and according to (17) from 0 to 0.6. The agreement seems to be bad for intermediate values of θ , and for a given θ , at large and small values of X/N .

In conclusion, the writers wish to thank Professor Sir Ralph Fowler for his continued interest and help.

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THE REACTIVITY OF THE CYSTINE LINKAGE IN KERATIN FIBRES.

PART IV. THE ACTION OF FORMALDEHYDE.

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The reaction of HCHO with the scleroproteins is one of considerable interest, and in the case of collagen fibres numerous investigations have been made.^{1, 2} Keratin fibres, however, have received much less attention, and little is known of the mechanisms involved in the combination of HCHO with wool and hair fibres. One of the earlier investigations of the reaction was made by Trotman, Trotman and Brown³ who estimated the amounts of HCHO combining with wool in acid and alkaline solutions. A more detailed study has been carried out by Bowes and Pleass⁴ who examined the effect of pH and deamination on the combination of HCHO with collagen, hair, and silk fibroin. Clark and Shenk⁵ studied the X-ray diffraction patterns of formalised gelatine, hair and silk. In all the proteins examined (with the exception of silk) definite changes in the X-ray diagrams were found after the materials had reacted with HCHO. The reaction of HCHO with feather keratin has been examined by Hegman⁶ who concluded that at ordinary temperatures no HCHO reacts with keratin between pH 1-6. Apparent fixation of HCHO in this range was said to be due to bisulphite binding substances formed during the digestion of the protein,⁶ plus residual free HCHO. From pH 6-8 reaction is said to be confined to the lysine present, while with low concentrations of HCHO the reaction above pH 8 is confined to arginine. Middlebrook and Phillips⁷ found that at 70° C., but not at room temperature, wool reacts with HCHO in solutions at pH 5-6. Wool that has reacted with HCHO at 70° C. does not react with NaHSO₃ to give —SH and —S—SO₃Na groups that are stable to water. It was concluded that the fractions of —S—S— sulphur in wool which react with NaHSO₃ to give water-stable

¹ Bowes and Pleass, *J. Int. Soc. Leath. Trades Chem.*, 1939, **23**, 365, 451, 499.

² Highbarger *et al.*, *J. Amer. Leath. Chem. Assoc.*, 1940, **35**, 11; 1941, **36**, 271.

³ Trotman, Trotman and Brown, *J. Soc. Dyers and Col.*, 1928, **44**, 49.

⁴ Clark and Shenk, *Radiology*, 1937, **28**, 355.

⁵ Hegman, *J. Amer. Leath. Chem. Assoc.*, 1942, **37**, 276.

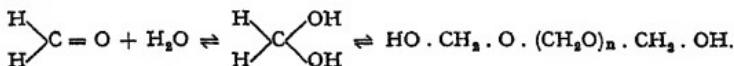
⁶ Riesser, Hansen and Nagel, *Z. physiol. Chem.*, 1931, **196**, 201.

⁷ Middelbrook and Phillips, *Biochem. J.*, 1942, **36**, 294.

—SH and —S . SO₃Na groups is also the fraction of the —S—S— that reacts with HCHO at pH 5·6 and 70° C.

Technological aspects of the reaction between HCHO and keratin have been studied in connection with attempts to protect wool against damage caused by scouring with soap and alkali.⁸ While more recently it has been claimed⁹ that treatment of tooth brush bristles with 20% HCHO in acid solution prevents hydrolytic "wet breakdown."

Numerous statements in the literature suggests that HCHO in aqueous solution mainly exists as the monohydrate methylene glycol CH₂(OH)₂. Measurements of absorption spectra do not reveal the presence of the carbonyl type of absorption,¹⁰ while the Raman spectra of aqueous solutions of HCHO correspond with those of ethylene glycols.¹¹ The excellent tanning effect of HCHO in non-aqueous solvents shows that the glycollic form of hydrated HCHO cannot be the tanning agent and supports the view of the active agent being the carbonyl monomeric form, as the glycol form is not present in these solutions. Auerbach and Barschall,¹² using M.Wt. determinations have shown that at least 12 hours are required for the polymethylene glycols to assume the monomeric form in equilibrium with HCHO.



Experimental.

Materials and Method.—Since the physical properties of keratin fibres are affected by exposure to light and air, only the root ends of human hair fibres, purified by extraction with alcohol, ether and water, were used in the following experiments. The load/extension curves of such purified hair were determined for 30% extension in distilled water at 22·2° C.,¹³ before and after treatment with HCHO. In each case, a 5 cm. length of the root part of the fibre was attached by means of dental cement to light glass hooks, and after being washed for 48 hours was calibrated by determining its load/extension curve in distilled water at 22·2° C. After standing overnight in distilled water, the fibre was treated with the reagent under examination, washed for 40 hours and then re-stretched. The buffer solutions employed were those of Walpole (pH 2·5), Kolthoff (pH 6), Palitzsch (pH 7·9) and Ringer (pH 10)¹⁴ used at 1/10 strength. A Cambridge Electrometer Valve pH meter was used to check the pH of each buffered HCHO solution immediately before use. In view of what has been said already about the condition of HCHO in aqueous solution, a time interval of at least 3 days was allowed to elapse between preparing solutions and using them. Supercontraction experiments were carried out in the manner previously described.¹⁵

Results.

(1) Effect of Time.—After a calibration stretch in distilled water fibres were refluxed with aq. solutions of 2% HCHO pH 5 for various lengths of time. The washed fibres were then stretched in distilled water, and the per cent. change in work calculated from the L/E curves. Blank experiments were performed using buffer solutions at pH 5. Fig. 1 shows

⁸ Kann, *Färber-Ztg.*, 1914, 25, 73; Henk, *Klepsig's Text-Z.*, 1936, 39, 670; Barr and Edgar, *Text. Res.*, 1937, 7, 175.

⁹ B.P. 502,853.

¹⁰ Schon, *J. Chim. Phys.*, 1929, 26, 72.

¹¹ Hibben, *J. Amer. Chem. Soc.*, 1931, 53, 2418.

¹² Auerbach and Barschall, *Ber.*, 1905, 38, 2833.

¹³ Stoves, *Trans. Faraday Soc.*, 1942, 38, 254.

¹⁴ Britton, *Hydrogen Ions*, London, 1932, pp. 217-223.

that maximum fibre strengthening occurs after treatment for 1 hour in boiling solution. Fibres treated with HCHO for longer periods show diminution in strength owing to the processes of hydrolytic breakdown exceeding the synthesis of new linkages. The remaining experiments were performed with boiling aq. solutions, the time of treatment being limited to 1 hour.

(2) Effect of pH.—Bowes and Please¹ examined the effect of pH on the amount of HCHO reacting with hair. Greater fixation was found to occur at high pH values than at low, and at all pH values hair fixed slightly more HCHO than could be accounted for by the basic groups of lysine and arginine. The reaction has now been examined with reference to the effect of pH upon the load/extension curves of treated fibres. Fig. 2 illustrates the results obtained for fibres treated for 1 hour at the boil with 2% HCHO pH 2-10. The lower curve shows that in the case of fibres treated with buffer solutions, hydrolytic breakdown of the fibre increases steadily from pH 3-10. Increasing hydrolysis of cystine linkages would be expected to give such a result. The fact that minimum damage occurs in the region pH 2-3, while Speakman and Coke¹² found a minimum at pH 5.5 almost certainly is due to the use by these investigators of buffer solutions of quite different composition from those used in the present work. The HCHO curve rises from pH 2-4 and remains comparatively

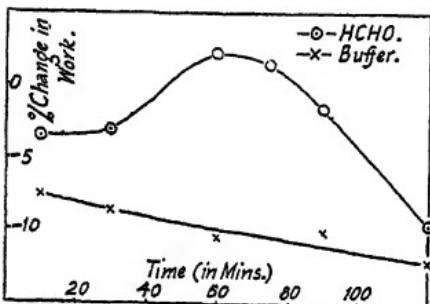


FIG. 1.

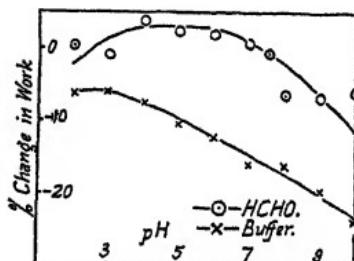


FIG. 2.

steady at a per cent. change in work of +3% until pH 7 is reached. Above this point fibre strength, as estimated by changes in the standard load/extension curves, diminishes. The difference between the two curves is a maximum in the neighbourhood of pH 7. Reference to the upper curve of Fig. 2 shows a greater deviation of readings from the mean than is found in the results for buffer treated fibres. This deviation (e.g. +5.5% at pH 10) is outside the limits of experimental error (i.e. $\pm 1.0\%$ resistance to extension) and appears to be connected in some way with the nature of the reaction between HCHO and keratin at high temperatures. The probable nature of some of the new linkages formed on treating hair with boiling solutions of HCHO is discussed in paragraph 4.

(3) Stability of HCHO Treated Hair.—A calibrated fibre was boiled for 1 hour in 2% HCHO at pH 6, and afterwards washed in running water for 40 hours. The fibre was then boiled in 1/10 K₂S₂O₈ for 1 hour, followed by a 40 hours' wash, and re-stretching in distilled water. The total reduction in the work required to stretch the fibre 30% of its original length was 67%. In the case of a fibre treated with buffer solution followed by K₂S₂O₈ the reduction in work was 87.7%. Fibres immersed in 2% HCHO pH 6 for 24 hours at 35° C., followed by 40 hours in running water, and treatment for 17 hours at 22.2° C. with 6.25% (V/V) 100 vol.

¹² Speakman and Coke, *J. Soc. Dyers and Col.*, 1938, 54, 563.

H_2O_2 $p\text{H}$ 7, suffered a reduction in work of 8.0 %. The result for a blank experiment was 12.0 % R.W. It appears, therefore, that treatment of hair keratin with HCHO does give a measure of protection against damage caused by oxidising agents.

The resistance to hydrolysis of formalised keratin was examined by treating calibrated fibres with 2 % HCHO $p\text{H}$ 6 for 1 hour at the boil, washing for 40 hours in cold running water, and re-stretching in distilled water. After an overnight rest, the fibres were boiled in distilled water for 1.8 hours, and the reduction in work determined. Blank experiments were performed using buffer solutions at $p\text{H}$ 6. Table I summarises the

TABLE I.

No. Hr. in Boiling Water . . .	1.	2.	4.	8.
% R.W. of HCHO fibres . . .	17.4	15.5	16.8	19.1
% R.W. of buffer fibres . . .	17.5	17.2	20.0	20.3

results. Under the conditions of experiment, therefore, HCHO does not appear to reinforce keratin fibres against the hydrolytic breakdown caused by boiling water.

(4) Nature of the New Linkages.—Theoretically,¹⁶ the possible centres of fibre reactivity are salt linkages, cystine linkages, imino and acid amide groups, —OH groups of serine and tyrosine, the guanidine groups of histidine, and the tryptophane side chains, while in boiling solutions of high acidity or alkalinity hydrolysis of peptide linkages will increase the number of —NH₂ and —COOH groups. The reactivity of these groups will, of course, vary with the conditions of temperature and $p\text{H}$, as well as with the nature of the reagent acting upon the fibre.

In an attempt to discover something of the nature of the reaction occurring between keratin and boiling solutions of HCHO, it was decided to determine the supercontraction in boiling 5 % $\text{Na}_2\text{S}_2\text{O}_8$ of fibres previously boiled for 1 hour in 2 % HCHO $p\text{H}$ 2-10.5. Three fibres were used for each $p\text{H}$ value and the mean values are shown in Fig. 3. The average supercontraction of normal, untreated samples of the hair used in these experiments is 25.5 %. Fibres which supercontract to a degree less than this must contain cross-linkages which are resistant to boiling $\text{Na}_2\text{S}_2\text{O}_8$. From this it follows that $\text{Na}_2\text{S}_2\text{O}_8$ resistant linkages are formed in fibres treated with boiling solutions of 2 % HCHO at $p\text{H}$ values < 3 or > 8. Between these two values few such linkages must be formed since the mean value of the supercontraction of treated fibres is 23 %. On comparing Figs. 2 and 3 it will be seen that although L/E curve experiments point to a greater net increase of cross-linkages in fibres treated with boiling HCHO $p\text{H}$ 6-7, than in fibres similarly treated at $p\text{H}$ 2, the latter fibres exhibit much greater stability to boiling $\text{Na}_2\text{S}_2\text{O}_8$, cf. the action of alkali in increasing fibre resistance to boiling $\text{Na}_2\text{S}_2\text{O}_8$, but diminishing

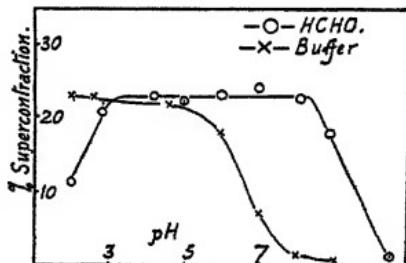


FIG. 3.

¹⁶ Gortner, *Outlines of Biochemistry*, New York, 1929, p. 030; Speakman, *Mather Lecture, J. Text. Inst.*, 1941, 32, T93.

resistance to extension.¹³ It can be concluded, therefore, that when keratin reacts with boiling solutions of HCHO pH 2-10, at least two types of new linkage are formed, one form being ruptured by boiling for 1 hour in 5 % $\text{Na}_2\text{S}_2\text{O}_5$, while the other type is not. An attempt was now made to determine how far the various reactive centres listed above were involved in formation of the new linkages.

(i) **Salt Linkage Amino-groups.**—When normal fibres which have been stretched in water to 30 % of their original wet length are allowed to stand for 17 hours in N/10 HCl at 22.2° C., followed by re-stretching in the acid, they are found to suffer a 30 % R.W. This increased ease of extensibility is caused by complete rupture of the salt linkages having taken place, due to displacement of aspartic and glutamic acids by the HCl. This fact was used to examine the extent to which the amino groups of salt linkages were taking part in the reaction of fibres with HCHO. The L/E curves of fibres treated with boiling solutions of HCHO pH 2-10 were determined as described in (2). These fibres were allowed to stand overnight in N/10 HCl at 22.2° C. and then were re-stretched in the acid. Table II gives the results obtained and shows that in fibres

TABLE II.

pH of Treatment . .	2.	3.	4.	5.	6.	7.	8.	9.	10.
% R.W. in N/10 HCl . .	17.3	20.3	24.7	20.3	20.7	19.9	19.2	22.5	10.4

boiled for 1 hour in 2 % HCHO pH 3-9 approximately 1/3 of the salt linkages are involved in the reaction. pH 4 appears to be an exception to this statement. After treatment at pH 2 and 10 just under 1/2 the total number of salt linkages are no longer in their original form. Recent work on the absorption of HCHO by proteins^{1, 17} supports Blum's view¹⁸ that condensation occurs between 1 molecule of HCHO and 2 $-\text{NH}_2$ groups with formation of $\text{R} \cdot \text{NH} \cdot \text{CH}_2 \cdot \text{NH} \cdot \text{R}$ linkages between main chains, although in alkaline solutions $-\text{N}=\text{CH}_2$ groups are also formed. It is suggested, therefore, that $-\text{NH} \cdot \text{CH}_2 \cdot \text{NH}-$ linkages are formed in all cases of fibres treated with boiling HCHO pH 2-10. Furthermore, since Fig. 3 shows that fibres treated with HCHO between pH 3-8 are but poorly resistant to boiling $\text{Na}_2\text{S}_2\text{O}_5$, the $-\text{NH} \cdot \text{CH}_2 \cdot \text{NH}-$ linkage must not be stable to this reagent.

Since a greater proportion of salt linkages are involved in the reaction between fibres and HCHO at pH 10, it is of interest to determine whether the extra salt linkages give rise to linkages other than $-\text{NH} \cdot \text{CH}_2 \cdot \text{NH}-$, such additional linkages accounting for the diminished supercontraction of the fibres (Fig. 3). If resistance to boiling $\text{Na}_2\text{S}_2\text{O}_5$ is due to linkages formed from amino groups, a fibre in which the $-\text{NH}_2$ groups have been removed prior to treatment with HCHO should show increased supercontraction in boiling $\text{Na}_2\text{S}_2\text{O}_5$ solutions. Accordingly, 3 fibres were completely deaminated in Van Slyke's reagent.¹⁹ Two 24-hour treatments were given, followed by a 72-hours' wash. The fibres were then boiled in 2 % HCHO pH 10.5 for 1 hour, in the presence of m. Na_2SO_4 to reduce swelling of the deaminated fibres. After being washed, the supercontractions of the fibres were measured. The mean result for the 3 fibres was 5.4 % supercontraction (cf. Fig. 3). Deaminated fibres which had been boiled for 1 hour in buffer solution at pH 10.5 were completely destroyed, so that it was impossible to measure their supercontraction. At pH 10.5, therefore, boiling solutions of 2 % HCHO react with keratin

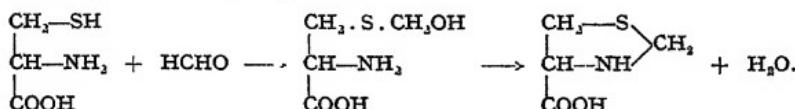
¹⁷ D'yachenko, *Org. Chem. Ind. (U.S.S.R.)*, 1938, 5, 745.

¹⁸ Blum, *Z. physiol. Chem.*, 1896, 22, 127.

¹⁹ Speakman, *J. Soc. Dyers and Col.*, 1934, 50, 341.

fibres to produce new linkages which are resistant to boiling 5% $\text{Na}_2\text{S}_2\text{O}_5$, and such new linkages do not involve the amino groups normally present in the fibre.

(ii) **Cystine Linkage.**—Above pH 3 initial hydrolysis of $-\text{S}-\text{S}-$ linkages, during the treatment of fibres with boiling HCHO solutions will give rise to $-\text{SH}$ and $-\text{S} \cdot \text{OH}$ groups (*cf.* buffer curve, Fig. 2). Now Ratner and Clarke²⁰ have shown that HCHO reacts with cysteine to form thiazolidine-4-carboxylic acid, reaction occurring first at the $-\text{SH}$ group, and being followed by ring closure.



The formation of thiol-HCHO addition compounds has been used by Challenger and Rawlings²¹ to explain the formation of methylated alkyl sulphides in $(\text{Et})_2\text{S}_2$ inoculated cultures of *P. brevicaule* Saccardo. HCHO (probably arising from glycine) is assumed to condense with formation of compounds of the type $\text{R} \cdot \text{S} \cdot \text{CH}_2\text{OH}$ ²² which then undergo reduction.

Furthermore, in the case of fibres treated with reducing agents so as to form $-\text{SH}$ groups, the damage resulting from such fission of $-\text{S}-\text{S}-$ linkages can, under certain conditions, be completely repaired by after-treatment with HCHO pH 8.²³ It is reasonable, therefore, to conclude that HCHO can react with $-\text{SH}$ groups to form linkages between the main polypeptide chains of the fibre.

Hence, in keratin fibres boiled with HCHO solutions above pH 3 it is probable that the $-\text{SH}$ groups formed by initial hydrolysis of the $-\text{S}-\text{S}-$ linkage, form addition compounds with HCHO. If such an addition compound is formed it may then condense with an amino-group from a basic side chain of an adjacent main chain. While such new linkages would give fibres increased resistance to extension, the observation²⁰ that thiazolidine-4-carboxylic acid is decomposed by NaHSO_3 suggests that the new linkages would not reduce supercontraction, a state of affairs which agrees with the results given in Figs. 2 and 3. In more alkaline solutions many more $-\text{SH}$ groups will be formed, and it is not unlikely that the addition compound would condense with a second $-\text{SH}$ group to form a linkage of the type $-\text{S} \cdot \text{CH}_2 \cdot \text{S}-$. The discovery of djenkolic acid in the djenkol bean of Java²⁴ lends support to this view of reaction between two $-\text{SH}$ groups, since the constitution of the acid,



shows it to be derived from HCHO and cysteine. The $-\text{S} \cdot \text{CH}_2 \cdot \text{S}-$ linkage would be expected to resist attack by boiling $\text{Na}_2\text{S}_2\text{O}_5$, and it is suggested that this is at least one type of resistant linkage formed in fibres treated with boiling solutions of HCHO above pH 9.

The lower curve (Fig. 3) shows that above pH 5 an increasing number of linkages resistant to boiling $\text{Na}_2\text{S}_2\text{O}_5$ are formed in fibres which have been boiled for 1 hour in the specified buffer solutions. Now Schöberl²⁵ has demonstrated that in neutral and alkaline solution the sulphenic acid $\text{R} \cdot \text{S} \cdot \text{OH}$ formed by hydrolysis of compounds containing the $-\text{S}-\text{S}-$ linkage breaks down to H_2S and an aldehyde. In the case of

²⁰ Ratner and Clarke, *J. Amer. Chem. Soc.*, 1937, 59, 200.

²¹ Challenger and Rawlings, *J. Chem. Soc.*, 1937, 871.

²² Levi, *Gazzetta*, 1932, 62, 775.

²³ Stoves, *Trans. Faraday Soc.*, 1942, 38, 261.

²⁴ van Veen and Hyman, *Rec. trav. chim.*, 1935, 54, 493; du Vigneaud and Patterson, *J. Biol. Chem.*, 1936, 114, 533.

²⁵ Schöberl *et al.*, *Annalen*, 1933, 507, 111; 1936, 522, 97.

the buffer treated fibres now under consideration a number of the —S . OH probably undergo this further reaction. Condensation of the —CHO groups so produced with —NII₂ groups would give rise to —N=CH— linkages²⁶ between the peptide chains, so stabilising the fibre against attack by Na₂S₂O₈.

In fibres treated for 24 hours at 35° C. with buffer solutions, the above reaction does not take place to any extent below pH 9.¹² At 100° C., however, the instability of the —S . OH group would be expected to be greatly increased, so that it is reasonable to assume that secondary reactions of —S . OH occur to an increasing extent in fibres boiled in buffers of pH 5-10. Initial —S—S— linkage hydrolysis, however, exceeds the rebuilding process, so that while the fibres are stabilised against attack by Na₂S₂O₈, they become increasingly more easily extensible (Fig. 2, lower curve).

Summarising, it is suggested that in fibres treated with boiling solutions of 2 % HCHO pH 3-10, the following linkages are formed by reactions involving the —S—S— linkage: —S . CH₂ . NH— at all pH values, and —S . CH₂ . S— above pH 9, while the resistance to supercontraction shown by fibres boiled in buffer solutions pH 5-10 is suggested to result from the presence of new linkages formed by secondary reactions of the —S . OH groups of hydrolysed —S—S— linkages. Below pH 3, boiling solutions of HCHO may function as acid reducing agents, so reducing —S—S— linkages to —SH groups which would then react with more HCHO to form stable —S . CH₂ . S— linkages by the mechanism already discussed. Such a reaction is compatible with the results of Figs. 2 and 3.

(iii) Other Groups.—In fibres boiled with HCHO in highly acid or alkaline solutions hydrolysis of main chain peptide linkages will give rise to additional amino groups which may react with HCHO to form new linkages.

Küntzel's theory²⁷ of methylene linkage formation between imino groups of adjacent main chains, however, is not supported by measurements of the amount of HCHO reacting with hair. If the reaction occurred to any extent then within the isoelectric region of hair keratin, where fibre swelling is a minimum, much more HCHO would be fixed by keratin fibres than is found experimentally.

Summary.

Determination of the load/extension curves of keratin fibres before and after boiling for 1 hour in 2 % HCHO pH 2-10 shows that at all pH values new linkages are formed, the greatest number, as estimated by the difference in behaviour of HCHO treated and buffer treated fibres, occurring in the neighbourhood of pH 7. At all pH values the amino groups of a proportion of the salt linkages take part in the reaction. In the case of fibres treated with boiling solutions of 2 % HCHO below pH 3 or above pH 9, linkages are formed which are stable to 1 hour in boiling 5 % Na₂S₂O₈. Fibres treated with boiling solutions of 2 % HCHO pH 3-8 contain relatively few of these linkages. Linkages formed by treatment for 1 hour with boiling 2 % HCHO pH 6 confer upon the fibre a partial immunity to attack by oxidising agents. No increased resistance, however, is shown to hydrolysis by boiling water. The probable nature of the new linkages is discussed.

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Leeds.*

²⁶ Phillips, *Nature*, 1936, 138, 121.

²⁷ Küntzel, *Angew. Chem.*, 1937, 50, 307.

THE REACTIVITY OF THE CYSTINE LINKAGE IN KERATIN FIBRES.

PART V. THE ACTION OF BENZOQUINONE.

By J. L. STOVES.

Received 6th July, 1943. As amended, 1st September, 1943.

In 1909, Meunier¹ claimed that wool could be strengthened by treatment with aq. solutions of benzoquinone. Meunier and Seyewetz² also found that quinone tannage was accompanied by the formation of hydroquinone, and therefore suggested that the benzoquinone oxidised free amino groups of the collagen with formation of hydroquinone, the oxidised grouping then combining with unchanged quinone. Later, Scharwin³ examined the reaction of benzoquinone with wool, horn, silk and other proteins. He concluded that the product formed is a substituted amino-quinone, the displaced hydrogen of the amino groups reducing further molecules of quinone to hydroquinone. More recently, Speakman and Coke⁴ have measured the increase in weight of wool after treatment with aqueous solutions of 2% benzoquinone at 100° C. The acid combining capacity of the treated wool was also determined. The increase in weight (16.8%) was much greater than the theoretical value (4.32%), assuming that all the basic side chains of wool were to react. Furthermore, the acid combining capacity of the wool showed that reaction with basic side chains was incomplete. It was concluded, therefore, that the reaction between wool and benzoquinone is not restricted to the basic side chains, and the formation of additional cross-linkages from acid amide, tyrosine and tryptophane side chains was suggested. Since polymerisation of benzoquinone occurs in aqueous solutions of benzoquinone at 100° C., the large increase in weight of benzoquinone treated wool obtained by Speakman and Coke may also be due in part to deposition of polymerised quinone within the fibres. In addition to its technical significance, the quinone reaction is of considerable biochemical interest, for Pryor⁵ has shown that the ootheca of *Blatta orientalis* is formed by interaction of a secretion of 2 glands, namely, a water soluble protein and a dihydric phenol. The phenol is oxidised, probably enzymically, to the quinone, which then reacts with the protein in a manner similar to the tanning of collagen by benzoquinone. The final rigid and resistant protein is said to be more stable than keratin. "Sclerotonin" has been proposed as the name of this new scleroprotein. The hardening of insect cuticle is a process analogous to the formation of the cockroach ootheca. Sclerotonin is similarly formed in the epicuticle, which is first secreted as a protein membrane and then "tanned" by the quinone reaction.

An earlier communication⁶ reported that under specified conditions keratin fibres damaged by treatment with reducing agents could be completely repaired by treatment with aq. solutions of benzoquinone. This reaction, together with the effect of benzoquinone on normal fibres, has now been examined further, the results obtained being described in the present paper.

¹ Meunier, Br. Fr. 48, 797; 1909.

² Meunier and Seyewetz, Comp. rend., 1908, 146, 987.

³ Scharwin, Z. Angew. Chem., 1913, 26, 254.

⁴ Speakman and Coke, Trans. Faraday Soc., 1939, 35, 258.

⁵ Pryor, Proc. Roy. Soc., B, 1940, 128, 378, 393.

⁶ Stoves, Trans. Faraday Soc., 1942, 38, 261.

Method.

The load/extension curves and supercontraction of human hair fibres treated with β -benzoquinone were determined by the standard methods used throughout this series of investigations. Buffer solutions were used as described in the previous paper, and where no pH value is stated the benzoquinone was used as a solution in distilled water.

Results.

(1) Effect of Concentration.—Calibrated fibres were boiled for 1 hour in benzoquinone solutions of various concentrations. After being washed for 24 hours in running water, the fibres were re-stretched and the % change in work measured from the L/E curves. Fig. 1 illustrates the results. It will be seen that increasing the concentration of reagent from 0 to 1 % greatly increases the number of new cross-linkages formed in the fibres, thereby causing a total change in work of 33 %. Increasing the concentration from 1 to 2 % produces only a slight increase (3 %) in % C.W., i.e. only 9 % of the change resulting from increasing the concentration from 0 to 1 %.

The remaining experiments were carried out using 2 % solutions of benzoquinone.

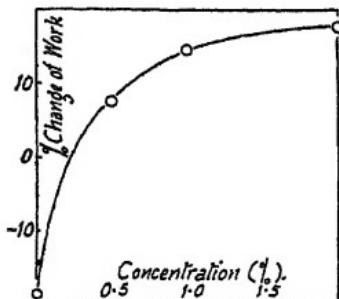


FIG. 1.

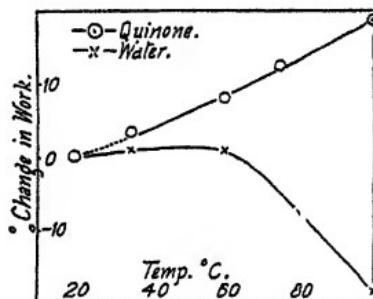


FIG. 2.

(2) Effect of Temperature.—After a calibration stretch in distilled water, fibres were treated for 1 hour with 2 % solutions of benzoquinone at various temperatures. At room temperature the low solubility of benzoquinone made it impossible to obtain a concentration of 2 %, consequently a saturated solution was employed at 22.2° C. Blank experiments were performed, using fibres treated with distilled water under the appropriate conditions. The results obtained are illustrated in Fig. 2, from which it will be seen that above 60° C. the difference between the two curves increases rapidly with further increase in the temperature of reaction, i.e. new linkage formation considerably outweighs the increased hydrolytic breakdown of cystine linkages. Future experiments were conducted with 2 % aq. solutions of benzoquinone at the boil, the time of treatment being 1 hour.

(3) Effect of pH .—The influence of pH upon the reaction of benzoquinone with keratin was examined by treating calibrated fibres for 1 hour with boiling 2 % benzoquinone pH 2.9. In preparing the solutions it was found that when the quinone was dissolved in buffers of $pH > 8$, the pH of the solution was invariably less than that of the buffer, e.g. 0.5 units at pH 9 and 1.1 units at pH 10. This was due to the rapid polymerisation of the quinone, which occurred with increasing rapidity as more alkaline buffers were used. The method adopted was to measure the pH of the quinone solution 10 minutes after preparation, and then use the solution immediately for treating the fibres. After boiling for 1 hour the pH of

alkaline solutions fell by anything from 0.5 to 1.5 units. Below pH 7, the initial pH of the quinone solution was that which would be expected for the buffer used. The pH of these solutions was but little affected by boiling.

After a 24 hours' wash the L/E curves of the treated fibres were re-determined, and the % change in work calculated. Fig. 3 illustrates the results, together with those obtained using buffer solutions alone. The pH values shown are the initial ones of the quinone solutions before boiling. Consideration of the two curves shows that from pH 2-7 synthesis of new linkages steadily increases. In cold solutions pH 2-7, benzoquinone is almost entirely in the monomeric form. On boiling the solutions, oxidative polymerisation occurs but there is always enough of the monomer present to react with the fibre, and cross-linkage formation increases as the pH of the solution rises. Above pH 7, however, polymerisation of the quinone occurs rapidly even at room temperature. On boiling such solutions, the concentration of reactive monomer rapidly falls. The polymer, probably for structural reasons, does not appear to react with the fibre, hence the much smaller number of new linkages formed in fibres treated with alkaline solutions of benzoquinone. The constitution of the polymer is not known. Diels *et al.*⁷ have shown, however, that pyridine can bring about polymerisation of *p*-benzoquinone to 2:5 di-(*p*-oxyphenoxo)-1:4 benzoquinone.

The reaction of *p*-benzoquinone with amines such as aniline,⁸ supports the view⁹ that quinone monomer reacts with the $-\text{NH}_2$ groups of proteins to form linkages of the type I. The % R.W. (13.6 %) in N/10 HCl of fibres boiled for 1 hour in 2 % benzoquinone shows that probably half the available salt linkages are involved in the reaction. This role of the amino-group receives further support from the observation that new linkage formation in fibres boiled in benzoquinone solutions diminishes steadily with increasing deamination of the fibres.¹⁰ Completely deaminated fibres, however, still show a slight

(2.7 %) increase in work after boiling in aq. solutions of benzoquinone.

(4) Effect of Pretreatment.—The $-\text{S}-\text{S}$ linkages of keratin fibres which have been treated with a reducing agent such as M/10 $\text{Na}_2\text{S}_2\text{O}_5$ for 17 hours at 22.2° C. are ruptured to the extent represented by a 10.8 % reduction in the work required to stretch the fibre 30 % of its original wet length. This damage can be completely repaired by overnight treatment with 1 % benzoquinone in distilled water at 22.2° C.⁶ Fibres which have been damaged to a similar extent (*i.e.* 9.2 % R.W.) by treatment with an oxidising agent, however, are only partially restored (3.5 % increase in work) by the same quinone treatment,¹⁰ the % increase in work being of the same order as that obtained on treating a normal fibre with benzoquinone under the same conditions, *i.e.* 4.7 %. In view of this result, and

⁷ Diels and Kassebart, *Ann.*, 1937, 530, 51; Diels and Priess, *ibid.*, 1939-543, 94.

⁸ Karrer, *Organic Chemistry*, Amsterdam, 1938, p. 532.

⁹ Stoves, *Thesis, University of Leeds*, 1938, p. 156; see Speakman, *Mathor Lecture, J. Text. Inst.*, 1941, 32, T93.

¹⁰ Stoves, *Trans. Faraday Soc.*, 1942, 38, 501.

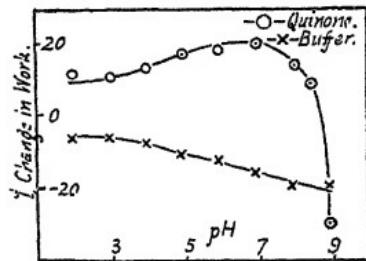
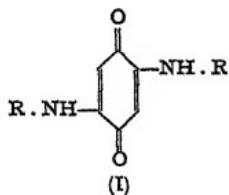
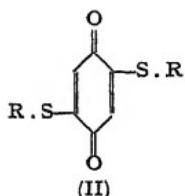


FIG. 3.



since amino groups would be expected to be equally available in all 3 cases, it is reasonable to conclude that the greater number of linkages formed in the first case is due to cross-linkage formation by reaction of the quinone with —SH groups produced by reduction of the —S—S— linkages of the fibre. No such groups would be present in an oxidised fibre. In view of Snell and Weissberger's work¹¹ on thiol-benzoquinone compounds, it is probable that the additional linkages formed in the case of bisulphite treated hair are of the type II. The reaction of benzoquinone with reduced keratin has now been examined from pH 2-7. Owing to the abnormal condition of the quinone solution above pH 7, the results obtained using such solutions are not strictly comparable with those given by acid or neutral solutions. Calibrated fibres were treated for 17 hours at 22.2° C. with



the reaction being performed in a slowly revolving shaker. After being washed for 24 hours, and re-stretched, the fibres received treatment for 24 hours at 22.2° C. with saturated aq. solutions of benzoquinone pH 2-7. The % change in work of washed fibres was finally determined from the L/E curves. Fig. 4 illustrates the results obtained. Maximum linkage rebuilding is obtained using solutions which would be expected to cause minimum fibre swelling.

(5) Stability of Benzoquinone treated Fibres. (i) Oxidation.—Fibres which had been boiled for 1 hour in 2 % benzoquinone solution, followed by 1 hour in boiling $\text{N}/10 \text{ K}_2\text{S}_2\text{O}_8$ were still 10.5 % more resistant to extension than were the original fibres. The result for a blank experiment was —90.3 % resistance to extension. Benzoquinone, therefore, confers upon fibres considerable resistance to attack by oxidising agents. Experiments in another connection also showed that fibres boiled in quinone were resistant to attack by 6.25 % 100 vol. H_2O_2 pH 7.

(ii) Hydrolysis.—An outstanding feature of quinone tanned leather is its resistance to boiling water. It was decided, therefore, to examine the effect of boiling water upon the resistance to extension of fibres which had been boiled for 1 hour in 2 % benzoquinone solution. Calibrated fibres were treated with benzoquinone, washed for 40 hours and re-stretched. After an overnight rest in distilled water, the fibres were boiled in distilled water for various lengths of time. A series of blank experiments was also performed. Table I summarises the results.

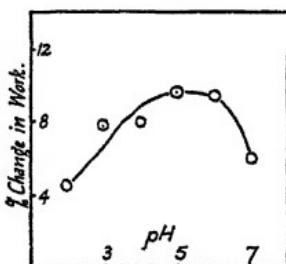


FIG. 4.

TABLE I.

No. Hr. in Boiling H_2O	1.	2.	4.	8.
Final % C.W. quinone	+ 20.2	+ 15.4	+ 11.3	- 0.6
Final % C.W. blank	- 14.4	- 14.6	- 18.0	- 25.0

The "tanned" fibres, therefore, are quite stable to 1 hour in boiling water. Further boiling causes a steady fall in resistance to extension, but even after 8 hours, fibre strength has only fallen to that existing before the

¹¹ Snell and Weissberger, *J. Amer. Chem. Soc.*, 1937, 59, 200.

original quinone treatment, and is much greater than that of a non-quinone treated fibre which has been boiled in water for 8 hours.

Summary.

The effects of concentration, temperature, and pH upon the reaction of β -benzoquinone with keratin fibres have been examined. Changes in the load/extension curves of fibres treated with aq. solutions at the boil, indicate that the reaction gives rise to the formation of new linkages within the fibres, thereby increasing the resistance of keratin to decomposition by hydrolysis and by oxidation. Using boiling solutions of 2 % benzoquinone, maximum formation of new linkages occurs at pH 7. In more alkaline solutions extremely rapid polymerisation of the quinone greatly reduces the number of new linkages formed, the effect being particularly marked above pH 8. Suggestions are made as to the nature of the linkages as well as to those formed by the action of benzoquinone upon fibres whose cystine linkages have been reduced by pretreatment with $\text{Na}_2\text{S}_2\text{O}_5$.

The author is indebted to the Directors of C. W. Martin & Sons Ltd. for facilities to carry out this work.

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THE ELECTROPHORETIC BEHAVIOUR OF CERTAIN HYDROCARBONS AND THE INFLUENCE OF TEMPERATURE THEREON.

By H. W. DOUGLAS.
(Communicated by W. C. M. LEWIS.)

Received 13th September, 1943.

In dealing with the relationship between the electrophoretic behaviour of pure organic compounds dispersed in aqueous media and their chemical structure it is desirable to start with bodies of the simplest constitution, *viz.*, the hydrocarbons.

Unfortunately, hydrocarbons are amongst the most difficult cases to investigate by reason of the thinness of their emulsions. Further, it is known that in the case of the low molecular weight paraffin hydrocarbons, *e.g.*, hexane, and also of benzene, it is not possible to obtain emulsions sufficiently stable to examine in the ordinary way. Such substances, however, may be examined by mixing them with suitable stable carriers; suitable carriers being liquids in which the substance in question is soluble, thereby producing composite droplets of known composition. The carrier must be of such a nature that its own electrophoretic characteristics are not too pronounced, for where this is the case the carrier masks to too great an extent the contribution made by the substance itself to the observed electrophoretic behaviour.* In short, the surface layer of the droplet must contain a sensible fraction of molecules of the substance under examination, for it is well known that the surface composition determines the electrophoretic behaviour.¹

Measurements have been made on the electrophoretic behaviour of emulsions both of single hydrocarbons and of binary hydrocarbon mixtures in aqueous media in the presence of o- or N. sodium ion, the purpose of

* Thus it has been found that composite droplets of hexane with sec. undecyl alcohol, containing up to some 90 molar per cent. of hexane, exhibit the same electrophoretic behaviour as droplets of the pure alcohol.

¹ H. A. Abramson, *Trans. Faraday Soc.*, 1940, 36, 9.

the electrolyte being to maintain a constant thickness of the electrical double layer.

Experimental.

The Mobility Determinations.—The electrophoretic mobility measurements were carried out by the macroscopic moving boundary method. The apparatus was similar to that described by Price and Lewis,² and capable of accurate temperature control ($\pm 0.1^\circ\text{C}$). The supernatant liquid and the dispersion mixture used were of the same ionic composition and $p\text{H}$; sucrose was added to the dispersion to give a 2% solution in order to maintain well defined boundaries.

Different $p\text{H}$ values were obtained by the use of various buffer solutions as described by Dickinson.³ The $p\text{H}$ values of the solutions were frequently checked potentiometrically using both a glass electrode and a hydrogen electrode to measure $p\text{H}$ values below $p\text{H} 8$; the latter electrode only was used for $p\text{H}$'s above $p\text{H} 8$.

Mobility- $p\text{H}$ curves were determined at 25° , 30° and 40°C . for dodecane, at 25° and 40°C . for paraffin wax, and at 25°C . for Δ^{1-2} octadecene. Also, the variations in the mobility of the composite droplets, containing increasing molar fractions of each of the substances hexane, benzene, cyclohexane and dekalin, have been determined at $p\text{H} 9$ and 25°C ., using dodecane as the carrier.

Purification.—As slight traces of impurity have a large effect on observed electrophoretic behaviour, special attention has been paid to the purification of the materials employed.

The hexane and cyclohexane used were B.D.H. "Spectroscopically Pure" products. They were washed with distilled water, dried and distilled (B.P.'s 68.7°C . under 754 mm. and 80.8°C . under 762 mm. respectively).

The sample of dodecane, as supplied by Fraenkel and Landau (Berlin), gave an emulsion having a mobility of $2.64\mu/\text{sec.}/\text{volt}/\text{cm.}$, towards the anode, at $p\text{H} 9$ and 25°C . It contained unsaturated compounds and was purified by shaking successively with concentrated sulphuric acid, aqueous alkali and distilled water. This treatment was repeated until a product of constant electrophoretic mobility was obtained. The hydrocarbon was finally distilled from sodium at reduced pressure, B.P. 78°C . under 7 mm. The final emulsion gave a mobility of 1.16 units at $p\text{H} 9$ and 25°C .

The original paraffin wax was Baird and Tatlock's "Specially Selected" wax (softening point *circa* 60°C .). An emulsion gave a mobility of 1.51 units at $p\text{H} 9$ and 25°C . The wax was purified by shaking with hot concentrated sulphuric acid at 90°C . until fresh acid remained uncoloured, then with hot aqueous alkali and finally to neutrality with distilled water. It was then recrystallised from A.R. ether until the mobility, 0.96 unit at $p\text{H} 9$ and 25°C ., was constant within the experimental error (*circa* 5%).

The initial Δ^{1-2} octadecene was a stored fraction of a sample used by previous workers in this laboratory.⁴ An emulsion gave a mobility of 4.08 units at $p\text{H} 9$ and 25°C . It was purified by repeated distillations at reduced pressure (*circa* 10 mm.) in a "Quickfit" all-glass apparatus, the middle fractions only from each distillation being used in the next stage. After five distillations a middle fraction of B.P. 176.8°C . under 14 mm. was obtained, and a further distillation left the mobility, 1.91 units at $p\text{H} 9$ and 25°C ., unchanged within the experimental error. This product had a B.P. of 176.8°C . under 14 mm., density $d_4^{25} = 0.7862$, and a refractive index $n_D = 1.4452$.

² Price and Lewis, *Trans. Faraday Soc.*, 1933, **29**, 775.

³ W. Dickinson, *ibid.*, 1941, **37**, 140.

⁴ A. W. Evans, *ibid.*, 1937, **33**, 794.

The benzene employed was Kahlbaum's thiophene free, "pro-analyse" product. It was distilled before use, B.P. 80·1° C. under 757 mm.

The initial dekalin, a B.D.H. product used by previous workers,⁵ had a mobility of 1·23 units at $p\text{H}$ 9 and 25° C. It was purified by treatment with fuming sulphuric acid, followed by aqueous alkali and then washed to neutrality with distilled water; it was then dried over sodium wire and distilled, B.P. 182·4° C. under 760 mm. An emulsion of the product gave a mobility of 1·01 units at $p\text{H}$ 9 and 25° C., unchanged by further treatment. This final product had a refractive index $n_D^{20} = 1\cdot470$, together with the boiling-point this constant indicates that *trans*-dekalin is produced by this treatment.

Preparation of the Emulsions.—Emulsions of paraffin wax were prepared both by the alcohol condensation method and by the steam-jet method; these methods have been described in papers by Williams⁶ and others. Emulsions of the other hydrocarbons and of the mixtures were prepared by a modification of the steam-jet method as previously employed. The modification consisted in the replacement of the single jet, of approximately 1 mm. internal diameter, by several of much smaller diameter, *circa* 0·1 mm. Using such a multiple jet and steam under a pressure of some 2 metres of water the emulsions prepared were much thicker and more stable than those prepared by either the original steam-jet method, the alcohol condensation method, or the homogeniser. Further, the method presents the minimum opportunity for the introduction of extraneous material. Using the modified steam-jet method the writer was able to prepare temporary emulsions of hexane and benzene; these broke rapidly, however, and after 24 hours were too thin for measurements to be made.

Hexane, benzene and cyclohexane each possess a small solubility in water. In view of the small amount, *circa* 1 c.c., of any particular mixture used in the preparation of its emulsions these slight solubilities might considerably affect the composition of the mixed droplets, and in particular their surface composition, if distilled water were used as the continuous medium. To overcome this difficulty the distilled water was saturated with the appropriate hydrocarbon by shaking therewith and standing 24 hours. Dodecane, the carrier employed, has a negligible solubility in water.

Results.

The results obtained at 25° C. for dodecane, paraffin wax (a mixture of solid paraffin hydrocarbons approximating to C_{28-30}), and Δ^{1-2} octadecene by the writer are given in Fig. 1 along with the data of Dickinson³ for octadecane. The results obtained for the composite droplets of hexane-dodecane, cyclohexane-dodecane and dekalin-dodecane respectively at $p\text{H}$ 9 and 25° C. are given in Fig. 2. Fig. 3 gives the mobility- $p\text{H}$ curve for pure dodecane at various temperatures; similar results were obtained for paraffin wax at 25° and 40° C. Above 40° C. measurements were not possible owing to experimental difficulties.

The mobility- $p\text{H}$ curves for the hydrocarbons dodecane (liquid), octadecane (solid), paraffin wax (solid) and Δ^{1-2} octadecene (liquid) show the same general characteristics as those obtained for other compounds in the same media.^{3, 6} At all but the lowest $p\text{H}$'s the particles are negatively charged and the mobilities towards the anode increase regularly with increasing $p\text{H}$; about $p\text{H}$ 9 the mobility tends to a limiting value. The effect of molecular structure on the mobility is best considered in this region.

It is generally accepted that the negative charge at the interface between an "inert surface" and water is due to the adsorption of hydroxyl

⁵ W. L. Guest and W. C. M. Lewis, *Proc. Roy. Soc.*, 1939, 170, 503.

⁶ G. C. Williams, *Trans. Faraday Soc.*, 1940, 36, 1042.

ions either directly or by the ionisation of a single layer of adsorbed water molecules. Either mechanism will account qualitatively for the general shape of the mobility- pH curves.

For hydrocarbon surfaces in contact with aqueous electrolyte it is likely that the electrical double layer is of the type postulated by Gouy.⁷

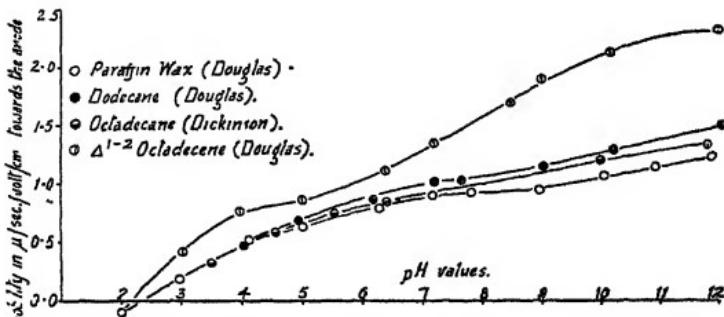


FIG. 1.—Mobility- pH curves for paraffin wax, dodecane, octadecane and Δ^{1-2} octadecene at 25° C. in the presence of 0.01 N. sodium ion.

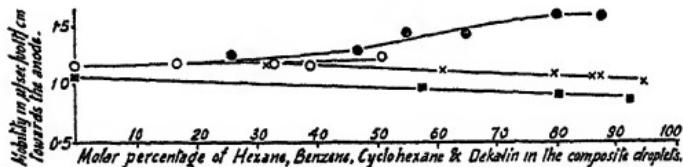


FIG. 2.—The mobilities, at pH 9 and 25° C., of hexane-dodocane, benzene-dodocane, cyclohexane-dodocane and dekalin-dodocane mixtures.

○ Hexane-dodocane. X Cyclohexane-dodocane.
● Benzene-dodocane. ■ Dekalin-dodocane.*

* The dekalin-dodocane mobility values have been reduced by 0.1 units in order to separate the plots.

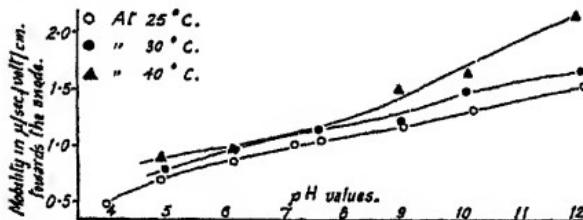


FIG. 3.—Mobility- pH curves for dodecane.

Assuming a regular variation in the electrophoretic behaviour of mixed droplets with increasing amounts of the hydrocarbon which would not, of itself, give an emulsion, the various curves in Fig. 2 have been extrapolated to give the following values for the mobilities, at pH 9 and 25° C., of the hypothetical emulsions of these substances. The values obtained are :—

Hexane	1.2 units.	Cyclohexane	1.03 units.
Benzene	1.65 units.	Dekalin	0.99 units.

⁷ Gouy, *J. Physique*, 1910, 9, 457.

Discussion.

The similarity in the mobilities at pH 9 and $25^\circ C.$ for the hydrocarbons hexane (1.2 units), dodecane (1.16 units), octadecane (1.15 units), and paraffin wax (0.96 units) indicates that all straight chain paraffin hydrocarbons would show substantially the same electrophoretic behaviour in a particular aqueous medium within the limits of the experimental error; thus their interfaces with water possess substantially the same affinity for hydroxyl ions. The close agreement between the extrapolated values for the mobilities of cyclohexane and dekalin and that measured directly for dekalin (1.03, 0.99, and 1.01 units respectively) indicates identical electrophoretic behaviour within the limits of the experimental error. The mobility- pH curve for these compounds at $25^\circ C.$ would lie slightly below that for dodecane. These cyclo-paraffin/water interfaces thus have a slightly smaller affinity for hydroxyl ions than the dodecane/water interface. The extrapolated value for benzene (1.65 units) lies considerably above the paraffin hydrocarbon value—indicating that the benzene/water interface has a greater affinity for hydroxyl ions than a paraffin hydrocarbon/water interface. Octadecene has an even higher mobility (1.99 units) at pH 9 and must adsorb hydroxyl ions to an even greater extent than a benzene surface in a particular aqueous medium.

Turning now to the effect of temperature upon the mobilities of dodecane (liquid) and paraffin wax (solid) emulsions it will be noted that the mobility at any particular pH increases with temperature, though the divergences between the curves are only small.

The corresponding zeta potential- pH curves have been evaluated by means of the expression

$$\zeta \text{ (in volts)} = \frac{4\pi\eta\mu}{D} \frac{1}{f(\kappa\alpha)}$$

where

μ is the mobility of the particles in $cm./sec./volt/cm.$

η is the viscosity of the medium in poise. The values * used were 0.0900 poise at $25^\circ C.$, 0.08007 poise at $30^\circ C.$ and 0.0656 poise at $40^\circ C.$

D is the dielectric constant of the solution. The values * used were 78.2 at $25^\circ C.$, 76.5 at $30^\circ C.$ and 73.1 at $40^\circ C.$. The effect of N./100 salt is very small (1 or 2 %) and has been neglected; the values given are for the pure solvent.

$f(\kappa\alpha)$ is Henry's function.⁸ In the present work the particles were of average radius (α) $5 \cdot 10^{-8}$ cm. For solutions N./100 with respect to electrolyte, this corresponds to a value 0.99 for Henry's function.

The zeta potential curves so calculated are given in Figs. 4 and 5 for dodecane and paraffin wax respectively. The zeta potential varies but little with change of temperature over the range 25° to $40^\circ C.$ Burton⁹ has recorded similar results for silver sols, for which the product mobility \times viscosity was approximately constant over the temperature range 3° to $40.5^\circ C.$

Treating the electrical double layers round the particles as equivalent to small parallel plate condensers, capacity C per unit area of the plates, then

$$C = \frac{D'}{4\pi\delta} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where D' is the dielectric constant within the double layer and δ is the distance between the plates, taken as the thickness of the double layer

* From the International Critical Tables.

⁸ D. C. Henry, *Proc. Roy. Soc. A*, 1931, 133, 106.

⁹ E. F. Burton, *The Physical Properties of Colloidal Solutions*, Table XX, p. 145.

calculated from the Gouy theory. For a particular aqueous medium—of fixed pH and salt concentration—the thickness $\delta \propto \sqrt{D'T}$ and hence the capacity of the electrical double layer will vary as $\sqrt{D'/T}$. The charge per unit area, q , is related to the potential, ζ , by the equation $q = C \cdot \zeta$, and thus for a particular aqueous medium

$$\zeta \propto \frac{q}{\sqrt{D'T}} \quad \dots \quad \dots \quad \dots \quad (2)$$

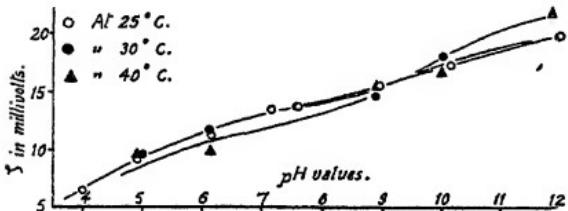


FIG. 1.—Zeta potential- pH curves for dodecane.

If Q_{OH} is the heat adsorption (measured in calories absorbed) per gram-ion of hydroxyl ions, then from thermodynamic considerations we may write

$$\log_e \frac{q_1}{q_2} = \frac{Q_{OH}}{RT_1 T_2} \cdot (T_1 - T_2) \quad \dots \quad \dots \quad \dots \quad (3)$$

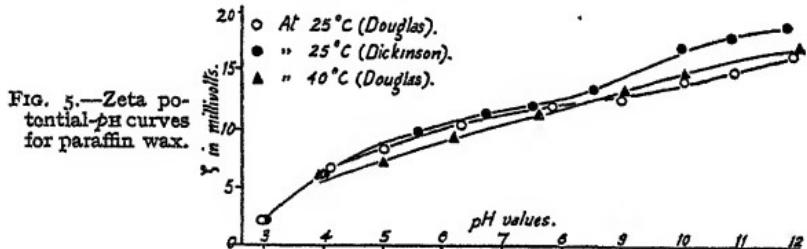


FIG. 5.—Zeta potential- pH curves for paraffin wax.

Substituting the proportionality (2), converting to \log_{10} , and rearranging

$$Q_{OH} = 2.303 \frac{RT_1 T_2}{(T_1 - T_2)} \cdot \log_{10} \left\{ \frac{\zeta_1}{\zeta_2} \sqrt{\frac{D'_1 T_2}{D'_2 T_1}} \right\} \quad \dots \quad \dots \quad \dots \quad (4)$$

By means of equation (4), assuming that ζ remains constant within the experimental error for the paraffin hydrocarbon/water interface over the temperature range 25° to 40° C., and that the variation in D' is the same as for the bulk value D , the values shown in Table I were obtained for Q_{OH} . The values obtained are of the expected order of magnitude, and the agreement between them is fairly good.

TABLE I

Temperatures in Degrees Absolute.		Ratio of Bulk Dielectric Constants.	Q_{OH} , Heat of Adsorption per gram ion OH ⁻ , as Calories Absorbed.
T_1 .	T_2 .		
298	303	$\frac{78}{76.5} = 1.02$	-955
303	313	$\frac{76.5}{73.1} = 1.05$	-739
298	313	$\frac{78}{73.1} = 1.07$	-715

Summary.

Electrophoretic mobility- pH curves have been determined for dispersions of dodecane, paraffin wax and Δ^{1-4} octadecene.

In order to obtain values for substances which do not of themselves form sufficiently stable emulsions, the artifice was adopted of forming composite liquid droplets thereof with a suitable carrier.

It was found that the affinity for hydroxyl ions of a hydrocarbon/water interface varies for different types of hydrocarbon. For the paraffin hydrocarbons dodecane and paraffin wax, practically coincident zeta potential- ρH curves were obtained over the range 25° to 40° C.; calculation gave the heat of adsorption of hydroxyl ions as approximately 800 cals. evolved per gram-ion of hydroxyl adsorbed.

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THE INFLUENCE OF SURFACE FILMS OF OIL ON THE EVAPORATION OF WATER.

BY R. W. POWELL.

Received 9th April, 1943.

The author has carried out a number of experiments to determine the laws governing the evaporation of water from saturated surfaces.^{1, 2} One problem which had given rise to this investigation related to the loss of moisture from meat carcasses during shipment and storage, and it was thought necessary to ascertain how the evaporation from a clean water surface compared with that from a surface contaminated with oil or grease. The results described in the present paper were obtained some time ago, and the subject would then have been pursued further had not other work intervened. In the meantime three other publications^{3, 4, 5} on the subject have been noticed, and accordingly it is felt that the publication of this account might be of interest.

The most recent work of Heymann and his collaborators^{4, 5} has related to the use of multimolecular films of oil as a means of preventing or reducing the evaporation of water from exposed water surfaces in arid climates. They found⁴ that films of paraffin oil of 1 to 2×10^{-4} cm. in thickness to which suitable spreading agents have been added will reduce the evaporation by 50 to 60 per cent. Reductions up to 99 per cent. were obtained with 0.5 to 1×10^{-4} cm. films of certain high boiling fractions of neutral oil of vertical retort tar. Their most recent paper⁵ deals with the stability of these multimolecular films of oils on water surfaces, and tabulated results are given showing that films of polymerised oil of considerable stability can be obtained, which for thicknesses of 5×10^{-4} cm. and 10×10^{-4} cm. reduce the evaporation into still air by 58 to 78 per cent. and 70 to 81 per cent. respectively.

Some years previously Jeppe and Segal⁶ had investigated the possibility of using oil films to lower the atmospheric humidity in deep South African mines. Their laboratory experiments, carried out at air velocities of 1000 to 1300 ft. per min., showed that films of fuel oil 25×10^{-4} cm. in thickness reduced the evaporation from an underlying water surface by about 85 to 90 per cent.

Hedstrand⁷ concluded that mono-molecular films had no effect on the

¹ Powell and Griffiths, *Trans. Inst. Chem. Eng.*, 1935, 13, 175.

² Powell, *ibid.*, 1940, 18, 36.

³ Sebba and Briscoe, *J. Chem. Soc.*, 1940, 106.

⁴ Docking, Heymann, Kerley and Mortensen, *Nature*, 1940, 146, 265.

⁵ Heymann and Yoffe, *Trans. Faraday Soc.*, 1942, 38, 408.

⁶ Jeppe and Segal, *J. Chem. Met.-Mining Soc. S. Africa*, 1933, 33, 131 and 397.

⁷ Hedstrand, *J. Physic. Chem.*, 1924, 28, 1245.

rate of evaporation from water, and Rideal⁸ showed that a surface contamination of this type did diminish the true rate of evaporation into a vacuum, but would not be expected to have any measurable effect in the case studied by Hedstrand for which the controlling factor was the rate of diffusion through the overlaying air film.

Sebba and Briscoe⁹ have developed a technique for obtaining comparative measurements of the rate of evaporation of water through monomolecular films into a constant current of dry air under conditions of controlled surface pressure. The interesting discovery is made that the resistance offered by these films to the evaporation of the underlying water is a highly specific property and that whereas under the conditions of their experiments films of egg albumin, cholesterol, oleic acid and elaidic acid offered practically no resistance, films of stearic acid, brassidic acid, arachidic acid, cetyl alcohol, octadecyl alcohol and *n*-docosanol can cause reductions amounting, in the case of the last-mentioned film, to 99 per cent. of the evaporation from a free water surface when the surface pressure exceeds a critical value.

Towards the conclusion of their paper mention is also made of some tests in which the water surface was covered by relatively thick films of lubricating oil. A film just thick enough to show the first interference colours caused a reduction of only 3 per cent. in the rate of evaporation, whilst a film so thick that interference films could no longer be seen caused a reduction of 73 per cent., showing, as the authors remark, that a much greater resistance to evaporation can be obtained with an appropriately chosen closely packed film one molecule thick than with an indicator oil film of the order of 100 molecules thick.

The present experiments relate to oil films having thicknesses ranging up to about 2.5 cm. The results confirm Sebba and Briscoe's conclusion as to the relatively low resistance to evaporation afforded by "coloured" oil films and further show that the degree of protection afforded by a thin film of oil increases as the air velocity is increased. It is also shown that there is an optimum thickness for a given oil for which the rate of evaporation from the underlying water surface has a minimum value.

Theory.

As already implied, in considering the general problem of the transfer of water vapour molecules through a film of oil into air allowance has to be made not only for the resistance imposed by the film itself, but also for that of the layer of air immediately above the oil through which the vapour molecules escape by diffusion. It is the diffusion through this air film which governs the rate of evaporation in the absence of any surface contamination.

Let t_a and t_o be the thicknesses of these oil and air films and c_w , c_o and c_a the vapour concentrations at the water-oil boundary, oil-air boundary and at the limit of the air film through which diffusion occurs. Then if E is the mass of water evaporated from a surface of area A , in S seconds and D_a and D_o the coefficients of diffusion of water vapour through air and oil respectively,

$$\frac{E}{S} = \frac{D_a A (c_o - c_a)}{t_a} = \frac{D_o A (c_w - c_o)}{t_o} \quad \quad (1)$$

The resistances of the air and oil films to evaporation under a unit concentration difference are given by $t_a/D_a A$ and $t_o/D_o A$ respectively. The value of D_a is about $0.25 \text{ cm.}^2 \text{ per sec.}$ Whereas no previous experiments appear to have been carried out to determine D_o , the present work leads to values of the order of $3 \times 10^{-5} \text{ cm.}^2 \text{ per sec.}$ t_o is a function of the air velocity over the surface, becoming smaller as the air speed is increased, thus the extent by which the rate of evaporation of water is affected by means of a superimposed film of oil should be least under still air conditions and should

⁸ Rideal, *ibid.*, 1925, 29, 1585.

become relatively greater as the air speed is increased. Thus the foregoing considerations show that the value of a film of oil as a preventative of evaporation from an underlying water surface should increase as the air speed over the surface is increased.

Experimental Determination of the Effective Thickness of the Air Film.

The present experiments were mostly of a relatively simple nature in which the rate of loss of weight was determined for surfaces contained in straight-sided glass dishes about 4 cm. deep and 6.8 cm. in diameter. The dishes were filled to within about 0.4 cm. of the brim. To determine the effective thickness of the air film, t_a , at various air velocities, two similar dishes containing water were placed on the floor of the wind tunnel used for the earlier evaporation work.¹ The temperature of the water in one dish was measured by means of a butt-welded thermocouple which could be introduced just below the surface. This temperature was used for the determination of c_w , the vapour concentration for saturation. The rate of evaporation from the other dish was determined from weighings made at the beginning and end of the experiment. The air velocity was measured and also the wet and dry bulb temperatures of the air approaching the dishes which enabled c_a to be derived. The values of t_a derived in this way and calculated from the equation

$$t_a = \frac{D_a A (c_w - c_a) S}{E}$$

are represented in Fig. 1 by the ringed points and the continuous line. Still air values obtained with the dishes on the floor of a closed box (about 1 metre cube) have been plotted at zero air velocity though they were probably influenced by convective air currents set up by local differences in temperature and vapour concentration. It is improbable that the air film is of uniform thickness, particularly since it will be influenced by the projecting rim of the vessel. Fig. 1 also contains data deduced from Figs. 5 and 6 of an earlier paper,¹ which relate to a surface 18.2 cm. wide and 24.3 cm. long down-wind, fitted with a stream-lined leading edge and subjected to a tangential wind stream. The curve drawn as a series of dashes represents the variation of the average film thickness with air speed, whilst the dotted curves serve to give some idea of how this film thickness increases as the air traverses the surface.

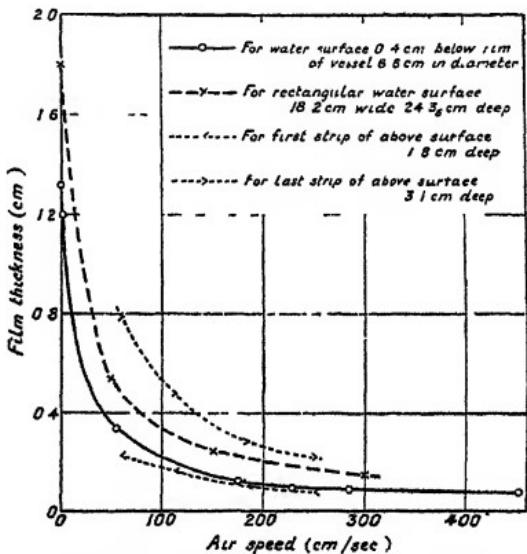


FIG. 1.—Dependence of effective thickness of air film on speed of air parallel to plane of surface.

Experiments to determine D_0 using thick oil films. Evidence for some other agency than diffusion, which assists the escape of water vapour through very thick films.

Determinations of D_0 were first attempted using relatively thick layers of oil, and these experiments led to an interesting result. Medicinal paraffin was used for a preliminary experiment. One vessel was filled to within about 1 cm. of the brim with oil only, and two others filled to a similar extent with layers of oil of 0.65 and 1.62 cm. thickness respectively,

floating on water. The three vessels were left in a still air enclosure and weighed periodically. Over a period of about three weeks there had been no loss for the vessel containing oil only, a loss amounting to 0.0018 gm. per day through the thinner oil sample and to 0.0025 gm. per day through the thicker oil sample. This result was surprising in that it indicated that the rate of loss of water vapour through the oil did not vary inversely as the oil thickness.

Similar tests, carried out in desiccators containing silica gel to absorb the water vapour, were later made for various oil thicknesses and at a series of steady temperatures, a vacuum oil and a mineral oil, AO.

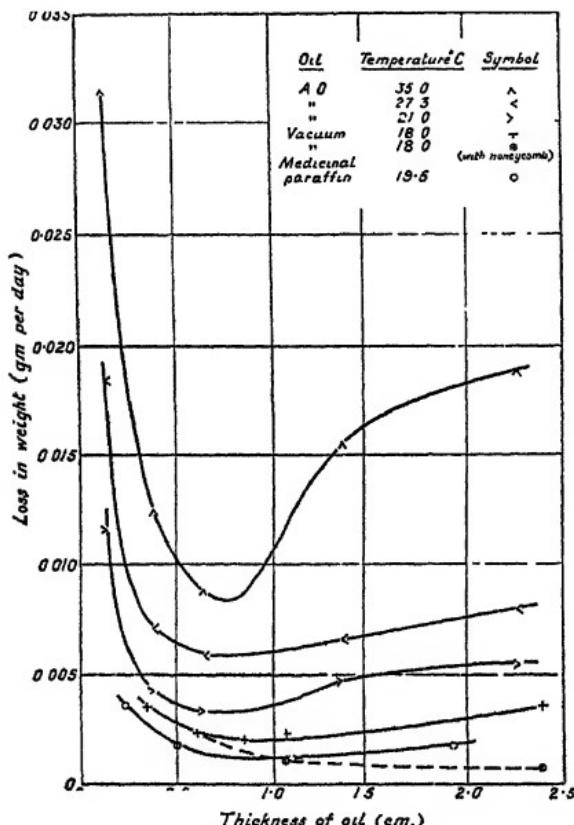


FIG. 2.—Rats of loss from water through oil films of various thicknesses.

which had been oxidised during use in steel quenching, being also studied. It will be seen from Fig. 2 that in each instance the rate of loss of water through the oil has a minimum value. This occurs when the oil thickness is of the order of 0.6 to 1.0 cm. There is some indication that the minimum occurs for smaller thicknesses of oil as the temperature is increased, and that the critical thickness is greatest for the medicinal paraffin and least for the oxidised quenching oil.

The complete results for the thick films of oil are set out in Table I. The last column of the table gives apparent values for the diffusion coefficients of the oils which have been calculated by means of equation (1),

the assumption being made that c_w is equal to the saturation vapour concentration of water at the enclosure temperature, and that $c_0 = c_a = \text{zero}$. In each instance the values are seen to increase with increasing thickness of oil, and it would seem that the reduction in the rate of transfer of water vapour molecules by pure diffusion which should result from an increase in the thickness of the oil layer is more than counter-balanced by an opposing effect, which becomes greater as the thickness of the oil is increased. A likely reason for an effect of this kind is that the transfer of water vapour is assisted by convection currents set up in the thick oil layers as a result of local changes of density. Such changes in density might arise from temperature inequalities, or result from the solution of air or water within the oil. Temperatures of the room in which the tests were made were maintained constant to within $\pm 0.1^\circ \text{C}$. In the tests with the oil AO freshly boiled water had been used to eliminate the possibility of air entering the oil from the water, but air may still have entered the oil from the surrounding atmosphere. So far it has not been possible to ascertain the exact reason for the convection currents being set up in the oil, or to detect any convectional movement, but the following results support the suggestion that the higher rates of water vapour transfer observed with thick layers of oil are due to a convective agency.

Honeycombs made from copper foil 0.017 cm. in thickness were so inserted in the vessel that they divided the oil layer into vertical cells about $0.6 \times 0.6 \text{ cm.}$ in cross section and about 0.2 cm. less in depth than the thickness of the oil layer.

It will be seen from the entries in Table I and the points in Fig. 2 shown as ringed crosses that with the honeycomb in position the augmented transfer is no longer obtained for increased oil thicknesses, and the experiment is regarded as confirming that the augmented transfer observed when no honeycomb is inserted is due to convection.

The values of diffusion coefficients derived from these tests agree fairly well with those for films 0.3 cm. or less in thickness, and presumably represent the true diffusion coefficients of water vapour through the oils. At about 20° C. these values range from $1.6 \times 10^{-5} \text{ cm.}^2/\text{sec.}$, for the medicinal paraffin, to $2.7 \times 10^{-5} \text{ cm.}^2/\text{sec.}$ for the oxidised mineral oil. The experiments carried out at higher temperatures indicate that the value of D_o increases relatively rapidly with increase in temperature. This increase is, no doubt, associated with the fact that the oil becomes less viscous at higher temperatures. The lowering of the viscosity should also allow convection currents to be set up more readily, which is consistent with the higher apparent values obtained for D_o with the thick films at high temperatures and for the tendency of the minima of the curves drawn in Fig. 2 to occur for lower oil thicknesses at higher temperatures.

The kinematic viscosities of the three oils were 141.4, 84 and 68 centistokes for the medicinal paraffin, vacuum oil and oxidised mineral oil respectively. From Table I it will be observed that the rate of diffusion of water vapour is roughly inversely proportional to the kinematic viscosity, and that a similar relation appears to hold for the increased vapour transfer attributed to convection.

Experiments using thin oil films.

The experiments described in the previous section for the determination of D_o occupied several days, owing to the small losses in weight which had to be measured. For the oxidised oils, which spread to form a uniform film on the surface of the water, it was thought that a more rapid determination could be made by using quite thin films and exposing the vessel to a high wind so as to make the effect of t_a negligible. The method was not entirely successful. Apart from inaccuracies in determining the quantity of oil used to form the film, some of the very thin films were unstable, and broke up into areas of non-uniform thickness, and also in

the presence of a wind the films tended to be blown towards the downstream edge of the vessel, so that the film thickness again varied across the surface. The method used was similar to that already described for the determination of t_s . Table II contains results obtained using films of the mineral

TABLE I.—EXPERIMENTAL DATA FOR THE DETERMINATION OF THE COEFFICIENT OF DIFFUSION OF WATER VAPOUR THROUGH OIL, USING THICK LAYERS OF OIL.

Oil.	Temperature (°C.).	Thickness (cm.).	Loss in Weight (gm./day.)	$10^5 \lambda$, Apparent diffusivity (cm. ² /sec.).
Medicinal paraffin	19.5	0.23	0.0036	1.6
		0.50	0.0017	1.6
		1.08	0.0011	2.2
		1.93	0.0016	5.8
Do.	30.3	0.23	0.0089	2.1
		0.50	0.0047	2.4
		1.08	0.0046	5.1
		1.93	0.0057	11.3
Do.	45.3	0.23	0.0227	2.5
		0.50	0.0119	2.8
		1.08	0.0150	7.2
		1.93	0.0160	14.8
Do. (with honeycomb)	21.2	2.50	0.0017	7.3
		2.50	0.00036	1.6
AO	21.0	0.13	0.0116	2.7
		0.37	0.0042	2.7
		0.63	0.0032	3.5
		1.35	0.0046	10.7
		2.26	0.0053	20.7
Do.	27.3	0.13	0.0184	3.0
		0.37	0.0070	3.1
		0.63	0.0058	4.4
		1.35	0.0065	10.6
		2.26	0.0078	21.2
Do.	35.0	0.13	0.0315	3.4
		0.37	0.0125	3.7
		0.63	0.0088	4.5
		1.35	0.0155	16.8
		2.26	0.0187	34.0
Vacuum oil	18.0	0.34	0.0035	2.5
		0.60	0.0025	2.8
		0.84	0.0019	3.3
		1.04	0.00225	4.8
		2.38	0.0034	16.7
Do. (with honeycomb)	18.0	1.04	0.0010	2.1
		2.38	0.0006	2.9

oil AO, and of the vacuum oil after it had been oxidised by heating in a dish exposed to air.

These experiments agree reasonably well with those using thick films, and suggest that a value of $D_s = 3 \times 10^{-5}$ can be assumed for the purpose

of estimating the effect which the presence of a film of such oil is likely to have on the rate of evaporation of water.

The continuous lines, drawn in Fig. 3 show the calculated effect of films 2.8×10^{-6} and 5.1×10^{-6} cm. in thickness. The dotted lines indicate the results of simple experiments when similar vessels were exposed to air streams, one containing water only and the other water protected by an

TABLE II.—EXPERIMENTAL DATA FOR THE DETERMINATION OF THE COEFFICIENT OF DIFFUSION OF WATER THROUGH OIL, USING THIN OIL FILMS.

Oil.	Temperature (°C.).	Thickness (cm.).	Loss in weight (gm./sec.).	$10^5 \times D_0$ (cm. ² /sec.).
Oxidised vacuum oil	22	0.0032	4.1×10^{-6}	3.3
	22	0.0016	7.4×10^{-6}	2.9
AO	—	—	—	—
	22	0.00018	53.2×10^{-6}	3.0
	22	0.00052	18.2×10^{-6}	2.9
	18	0.0007	14×10^{-6}	3.3

oil film. In such a test the results are not strictly comparable as the free water surface for which the evaporation is greater will assume a lower temperature.

It has not yet been possible to repeat the test and to include a measurement of surface temperature, and the fact that no allowance has been made for this difference in temperature probably explains the lack of complete agreement between calculation and experiment.

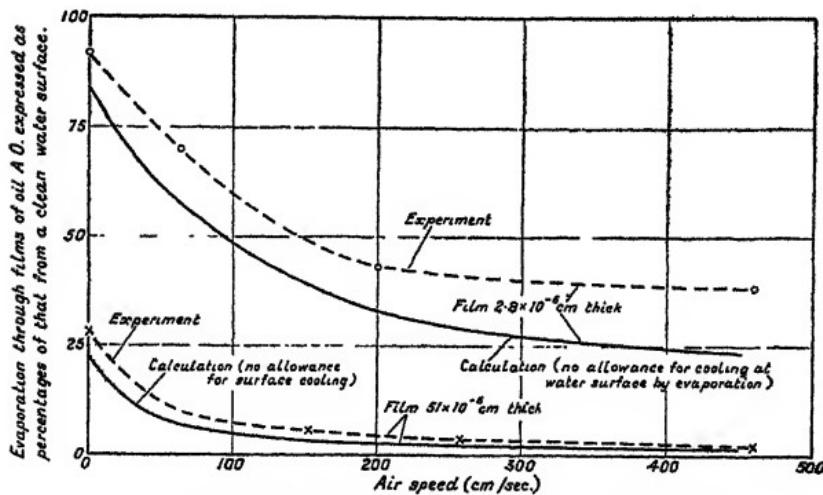


FIG. 3.—Effect of air speed on evaporation from oil covered surfaces.

Conclusion.

The present results suffice to show the general nature of the influence of oil films on the rate of evaporation of water. They are in reasonable agreement with the results, using oil film, obtained by Sebba and Briscoe and by Heymann and Yoffe, and with the general conclusion that the use

of such mono-molecular films causes but little reduction in the rate of evaporation from an underlying water surface, but that the reduction due to multi-molecular films of oil can become appreciable. It has been shown that the reduction becomes relatively greater as the air velocity is increased, and that the order of the effect can be estimated from a knowledge of the diffusion coefficients of water vapour through air and oil.

This investigation was carried out in the Physics Department of the National Physical Laboratory as part of the programme of the Food Investigation Board, and this paper is published by permission of the Department of Scientific and Industrial Research.

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REVIEWS OF BOOKS.

Elementary Physical Chemistry. By RANDALL AND YOUNG. (Randall & Son, 2512 Elina St., Berkeley, Calif., U.S.A., 1942. Pp. xiv + 455. Price \$ 4.50.)

This is an original work, set out in an original print. Its 32 chapters cover a wide range of modern and classical physical chemistry at a standard suited to the needs of the first year Honourman or the second year Honourman who desires to revise his knowledge of the fundamentals ; indeed, the post-graduate researcher who has become a little rusty in certain branches of his subject will find the book invaluable. The advanced physics student will find in a study of the text an excellent introduction to those problems in physical chemistry which so often overlap his own peculiar studies.

The theoretical expositions are clear, concise and arresting ; the descriptions of experimental work are full enough to be interesting and are accompanied for the most part by very clear line-drawings ; the 694 exercises provide material enough and to spare on which the student may try his strength and thereby materially increase his skill.

The treatment is up to date in its outlook but by no means neglects older work of importance, and the many and detailed references to the literature make easy and pleasant the task of the student who desires to consult the original sources. Indeed, the whole atmosphere of the book is that of the enquiring mind and should provide a healthy stimulus to the student to think for himself.

Some things must be taken and some left, but it is odd that there should be no reference to the parachor, and that the temperature variation of surface tension should be treated by way of the Föltvös equation without any consideration of the well known power law, $\gamma = \gamma_0(1 - bt)^n$.

The book is produced in imitation type-script. It is perfectly legible but demands a certain effort in reading until one becomes accustomed to the script. It is difficult to see why this mode of presentation should have been adopted.

The book may be heartily commended.

A. F.

MODES OF DRUG ACTION.

A GENERAL DISCUSSION.

Friday, 24th September, 1943.

A GENERAL DISCUSSION of the Faraday Society was held at The Hotel Rembrandt, London, S.W. 7, on Friday, 24th September, 1943, from 10 a.m. to 5 p.m. to discuss "Modes of Drug Action".

The President, Professor E. K. Rideal, occupied the Chair throughout the meeting. Some 250 members and guests of the Society were present. Luncheon was taken in the Hotel during an interval in the meeting. At the conclusion of the meeting thanks were accorded with acclamation to the Imperial College of Science for providing the epidiascope and other conveniences for the meeting at the hotel, as well as to the authors of the papers which had stimulated so useful a discussion.

The papers submitted in Advance Proof for discussion and the report of the discussion thereon appear in the following pages.

GENERAL INTRODUCTORY ADDRESS.

By SIR HENRY DALE.

The Faraday Society have honoured me with an invitation to open the proceedings at this day's Conference, and I have gladly accepted it; and I have done so the more gladly on account of the association of to-day's proceedings with the memory of my own old teacher and greatly honoured friend, the late Sir William Hardy. I am glad also to have the opportunity of adding my voice to those of other research workers in medicine and pharmacology, in welcome of the growing interest shown by physical chemists in many of our central problems. As evidence of this, we find the Faraday Society giving a day to the discussion of the actions of drugs, and we have the leaders of some of our chief schools of physical chemistry, with their co-workers, contributing to what promises to be a varied and illuminating discussion. It is almost a commonplace to say that any account of the life process, in its various manifestations, which science may eventually be able to present, will be written in terms of extremely complicated and labile physico-chemical systems. When we study the effects of chemical substances on different vital activities, then, and try to understand how these are modified, suspended or abolished by what we call pharmacological actions, we shall certainly need all that physical chemistry can contribute to our effort to understand what is happening. We are glad, accordingly, that this discussion is being held, and grateful to the Faraday Society.

Having said this, I hope that it will not seem grudging or presumptuous if I venture to suggest that those of us who have hitherto approached these problems, whether from the side of biology or of chemistry—and certainly myself no less than others, when I have rashly waded up to the short limit of my depth in these difficult waters—have tended almost inevitably to oversimplify the issue. I suspect that we have tried to attribute to such parallels between physico-chemical properties and pharmacological action, as we can observe in homologous series, a significance beyond what they can properly bear. Significance, of course, these parallels have; since any kind of vital process is dependent on

change in complex physico-chemical systems, the *intensity* of a particular action upon it, observed in an homologous series, is likely to be conditioned by some physico-chemical property that waxes and wanes again as we ascend the series ; and we seem, often enough, to have several such properties to choose from, with maxima at the same member of the series. The point which I wish to emphasise, however, is that this coincidence of maximum activity with a maximum of oil-solubility, or of activity on interfacial tension at a particular type of surface, may not throw any light at all, in the present state of our knowledge, on the specific appearance in that series of the physiological activity which we are studying, and which may be a highly specialised and an extremely complicated one. A good example of my meaning recurs in the papers to be presented by Dr. Schulman and Dr. Ing, both of whom happen to cite the interesting maximum of oestrogenic activity at the di-ethyl substitution stage in the series of dihydroxystilbenes. Dr. Ing is interested in this maximum from the point of view of structural chemistry, and Dr. Schulman in its coincidence with the form most actively adsorbed on a protein interface. Now I am certainly not suggesting that this coincidence is not of interest and significance ; but I do venture to urge that we should not allow ourselves, even subconsciously, to assume that it even begins to account for the occurrence, in this series as a whole, of the highly specific and complex activity, which we term oestrogenic. It is true that the formula of such a disubstituted stilbene can be written on paper in a shape recalling the carbon skeleton of the natural oestrogenic hormones ; but that, again, does not begin to tell us why the presence in the circulation of a trace of such a hormone, or of one of the members of the series under discussion, specifically initiates the complicated train of events in the mucous membrane of the female genital tracts which constitute what we call oestrus. That surely is not a general property of substances which are powerfully adsorbed on protein interfaces. All these parallels between structure, or physico-chemical properties, and special types of activity are of alluring interest and will, assuredly, provide data of great value for an eventual understanding of the problem, provided that we do not lose hold of the fact that its central core is still biological, and therefore of such complexity as still to be hardly tangible.

Paul Ehrlich, the real initiator and great pioneer of that side of to-day's subject which deals with the chemotherapy of infections, used to insist on the essentially biological nature of the problem, and to claim the initiative for the medical biologist. Yet the conceptions from which he sought to construct a framework of hypothesis, were largely derived from structural organic chemistry, and particularly from that of the dye-stuffs with which he was most familiar. And here again, it seems to me that the use of terms such as Ehrlich introduced, and others since his time, has its value as a scaffolding for ideas, provided that we remember that to label a phenomenon is not to reveal its nature. Dr. Ing alludes to the remarkable specificities of certain chemicals for physiologically effector cells—nerve, muscle and gland cells—and the association of these with innervation by different parts of the autonomic nervous system—surely one of the most fascinating of pharmacological mysteries, and one which remains a mystery, even with our present knowledge of the physiological intervention of adrenaline and acetylcholine in the transmission of different nervous effects. It is a mere statement of fact to say that the action of adrenaline picks out certain such effector-cells and leaves others unaffected ; it is a simple deduction that the affected cells have a special affinity of some kind for adrenaline ; but I doubt whether the attribution to such cells of "adrenaline-receptors" does more than re-state this deduction in another form.

Of great interest, again, is the switch-over as we ascend the "onium" series from predominant, selective stimulation to an equally selective paralysis of the same types of nerve cells and endings ; and this change

may legitimately be compared with a progressive change in various physico-chemical characters in the series. It seems to me, however, that, when we come to consider the basis of this selective action, we must not ignore anomalies, which, in the end, may prove to be more significant for any final conception than the regularities. The really fascinating problem, I suggest, is to be found in the fact that tetramethylammonium salts have a selective stimulant action closely similar to that of nicotine, of cytisine, and of lobeline, natural alkaloids which are not onium salts at all, and which are not remarkably similar to one another in molecular configuration. What is the property common to these, which gives them, in common, this highly selective activity? To say that they all have affinity for the same chemoreceptors is merely to restate the observed facts or, if it means more, to go without warrant beyond them.

Dr. King justly draws attention, I think, to the interest of the facts obtained by the study of drug-resistant strains, selectively bred out, as it were, by dosage too low to effect a permanent cure of an infection. The mention of such matters brings to mind the great loss to the study of chemotherapy in this country entailed by the recent death of our distinguished colleague and brilliant leader in this field of enquiry, the late Prof. Warrington Yorke. Knowing that he was a doomed man, Yorke used himself to the very limit of his waning strength to serve the cause of our country and its allies. Prof. Yorke, and others who worked with him, or have since followed the trail, have been able to show that trypanosomes thus made resistant to a group of arsenicals have lost the affinity for them, which enables normal trypanosomes to extract these compounds from a surrounding fluid. The fact that other organic arsenicals are still fully active on these resistant trypanosomes, is interpreted by the presence in these compounds of lipid-soluble groups. The trypanosomes which have thus been made resistant to atoxyl have also, as Ehrlich and his co-workers discovered, become resistant to acridine dyes like acriflavine, which no longer stain them as they do normal trypanosomes; but when Dr. King interprets this event as meaning that atoxyl and its analogues, on the one hand, and the acridine dyes on the other, are "substantive for the same type of structure in the trypanosomes," I am inclined to ask whether this does more than state in other terms the observed and surprising fact. And here I should like to raise the question, whether the recently observed possibility, of producing from normally sensitive cocci strains which have acquired a resistance to sulphonamide derivatives, may not present the opportunity for a direct attempt to discover something more definite about the chemical basis of such resistance. Unlike trypanosomes, such bacteria might, I suggest, be grown on a scale sufficiently large to enable some quantitative data to be obtained concerning certain constituents of the resistant and normally sensitive strains.

I hope that my remarks will not appear to be wholly critical and discouraging; that is certainly not my feeling or my intention. On the contrary, I feel that the present position of the subject of this Conference represents a tremendous advance on that of only a few years ago. We shall have abundant evidence in this discussion of the different kinds of technique and the different orders of conception which are now being brought to bear, in a convergent attack on a problem to which, even quite recently, the only method of approach seemed to be that of hit or miss, an empirical and almost undiscriminating trial of any accessible derivative of a substance in which, whether by planned investigation or sheer accident, a particular type of activity had been discovered. But now, in place of vaguely conceived chemoreceptors, labels for observed but unexplained affinities, it begins to be possible to think in terms of interference with activities of vital enzyme systems, whether by blocking the action of co-enzymes, or supplanting essential substrate molecules on the specific surfaces of enzymes. We shall hear from Sir Rickard Christophers about the respiratory enzymes of malarial parasites and the effects on them of

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antimalarial agents ; and there is the recent evidence about the mode of action of the sulphonamides and other bacteriostatic agents, as described by Fildes, Woods, MacIlwain and others, and discussed also to-day by Dr. King, in relation to the action of arsenoxides.

Then there are special problems, like those of the insecticidal actions discussed by Dr. Hurst, who has the advantage that he can skin his parasites and examine the separated cuticle for its properties as a physico-chemical system ; or that of the special properties, discussed by Dr. Lourie, which enable a trypanocidal agent to pass the so-called blood-brain barrier and become effective on trypanosomes infecting the brain. These may serve to illustrate the almost infinite complexities of the problem, viewed as a whole, on the biological side, and the need, if I may relapse into warning, for care not to assume too general a significance for the results obtained with a particular biological index, or an artificially simplified physico-chemical system or model. The present convergent attack, from so many special aspects of knowledge, gives, I believe, the highest promise of rapid and ordered advance in a field in which even opportunist and guerrilla tactics have already, and surprisingly, achieved results of such great practical importance.

INTRODUCTORY ADDRESS.

PART I. BIOLOGICAL ASPECTS: THE ANTAGONISM OF DRUGS.

By J. H. GADDUM.

Communicated on 24th September, 1943.

I should like to start by paying a tribute to Professor A. J. Clark. The title of this discussion is almost identical with that of a book which he wrote, and which, together with his article on General Pharmacology in *Heffter's Handbuch*¹ has been a great source of inspiration and information to all who are interested in pharmacology: I shall refer to them frequently.

The word drug means different things to different people. Many only use this word when they are speaking of dangerous drugs, such as opium, which lead to addiction. The pharmacologist likes to think that it means any substance which is applied to living matter, in order to see what effect it will have, and of course that means that there are very few substances which have not qualified as drugs at one time or another.

There are many modes of drug action. Some drugs act osmotically, some as acids or alkalis, or oxidising or reducing agents or by increasing the permeability of surfaces or precipitating proteins; some drugs act specifically on enzymes and some by quite unknown methods. We shall have a chance to discuss some complex modes of action this afternoon.

Many of the more interesting properties of drugs depend on the factors which cause them to concentrate at their site of action and several papers to-day are concerned with this process. Dr. Lourie is interested in the uptake of drugs in the central nervous system, Dr. King with their uptake by trypanosomes, and Dr. Hurst with their uptake by insects.

The actions of narcotics were discussed by this Society in 1937.² They are mostly simple aliphatic compounds which cause a reversible depression of living tissues. Their action depends on their general physical properties which cause them to concentrate on surfaces and in lipoids. The exact reasons for this concentration have been much discussed, but comparatively little is known about how these drugs depress living tissues once they have accumulated on their surfaces.

According to Dr. King³ phenylarsenoxide is taken up by trypanosomes in much the same way as narcotics are taken up. The uptake of atoxyl, and other drugs to which trypanosomes become resistant, depends on more specific chemical properties, and the same is true of many of the more interesting drugs, which combine specifically with tissues. Dr. King's other class of arsenical drugs are those which are comparatively inactive and are perhaps not concentrated at all.

I do not propose to review all possible modes of drug action, but to concentrate attention on the antagonism of drugs with reversible actions, since many recent developments are based on the quantitative study of antagonism, and there is undoubtedly much more work to be done in this field.

An antidote may counteract the effects of a poison in various different ways, the two most important of which are by neutralisation and by competition. It may either neutralise the poison by combining with it and forming an inert compound, or it may compete with the poison for chemical groups which are in some way essential to living tissue.

¹ Clark, *Heffter's Handbuch. exp. Pharmak. Ergänz. 4* (Springer, Berlin, 1937).

² *Trans. Faraday Soc.*, 1937, 1057.

³ *Vide infra*, 383.

Antagonism by Neutralisation.

An example of an antidote which acts by neutralisation is provided by compounds containing —SH groups, which counteract the effects of Hg and other heavy metals, and of organic arsenic compounds. It was shown, in 1908 by Chick¹ and has repeatedly been confirmed¹ that the action of mercury on bacteria can be reversed by treating the bacteria with H₂S. The initial reaction between the bacterium and the mercury is evidently reversible, though irreversible changes take place later. In the case of spores the reversible phase may last a week.

Soon after the last war Voeghtlin² and various collaborators were studying the actions of aromatic arsenic compounds in the chemotherapy of trypanosome infections. They showed that the action of trivalent arsenoxides of the form R—As=O could be directly observed by watching the movements of the trypanosomes under a microscope. When the arsenical was added, even in low concentrations, the movements ceased. This crude method of observing the effects of drugs gave interesting information. New methods, such as those described by Sir Rickard Christopher³ will doubtless give much more information.

The effect of trivalent arsenicals on the movements of trypanosomes was antagonised by adding any one of a number of SH— compounds. The same effect was demonstrated *in vivo*, by injecting SH— compounds into infected rats 1 minute before the injection of arsenoxides. This caused a delay in the disappearance of trypanosomes from the blood. It was also shown that SH— compounds prolonged the life of rats which had received a lethal dose of arsenoxide. This work has been confirmed and extended.^{1, 4} Voeghtlin believed that the arsenoxides were working by combining with the SH— groups which could be detected in the trypanosomes by the nitroprusside test. There can be little doubt that this combination takes place, since SH— groups have a particularly high affinity for arsenicals, but when this theory was advanced there was no direct evidence that the loss of free SH— groups would harm the organisms.

Fildes⁵ has shown that the action of Hg on *Bact. coli* is also antagonised by various SH— compounds, and has suggested that Hg also acts by combining with SH— groups in the organisms. The affinity of SH— compounds for Hg is of course great and has earned for them the title of mercaptans, but Fildes points out that the evidence is now fortified by work on the nutrition of bacteria. Dr. Fildes has taken a leading part in this work himself and it is unfortunate he is unable to give an account of it to-day (*cf.* Fildes⁶). *Bacterium coli* can grow when the only source of nitrogen in the medium is ammonia, but *B. typhosum* cannot grow, except when certain amino acids are added. Both organisms contain these amino acids as an essential part of their structure, but one can synthesise them from ammonia and the other cannot. In Fildes's terminology these amino acids are "essential metabolites" for both organisms; they are "growth factors" for *B. typhosum*, which cannot synthesise them, but not for *B. coli* which can. These investigations have thrown much light on bacterial metabolism, since some organisms will only grow when supplied with very elaborate growth factors.

It has been shown that moulds⁷ and *staphylococcus*⁸ and presumably other cells as well can obtain sulphur from any one of a variety of organic SH— compounds, presumably by converting them into cysteine, but cannot grow at all without SH— compounds. Further references to

¹ Chick, *J. Hyg.*, 1908, 8, 92.

² Walker, *Biochem. J.*, 1928, 22, 292.

³ Fildes, *Brit. J. exp. Path.*, 1940, 21, 67.

⁴ Fildes, *Lancet*, 1940, i, 955.

⁵ Volkonsky, *Ann. Inst. Pasteur*, 1934, 53, 76.

⁶ Fildes and Richardson, *Brit. J. exp. Path.*, 1937, 18, 292.

⁷ Voeghtlin, *Physiol. Rev.*, 1925, 5, 63.

chemical evidence of the importance of SH— compounds have been given by King.⁹ There is thus good evidence not only that Hg is likely to combine with SH— compounds, but that this combination will inhibit growth. According to Fildes removal of SH— compounds is the essential cause of the inhibition of growth by Hg.

Quantitative Theory of Neutralisation.

The quantitative relations between the concentrations of the poison and its antidote which just neutralise one another cannot be very accurately measured, but they can be studied over a wide range of concentrations. Voeghtlin found that the concentration of antidote had to be 10-20 times as great as the chemical equivalent of the poison. Fildes found that the corresponding ratio was 1·5-2 for glutathione and 6-12 for thiolacetate, and points out that this difference cannot be due to a difference of stability, since thiolacetate is more stable than glutathione under the conditions of the experiment. It seems likely that the difference is due to a difference in the dissociation constants of the compounds formed by combination of Hg with the two different antidotes.

Calculations may be based on two different fundamental assumptions. In the first place it may be assumed that it is necessary to use enough antidote to reduce the concentration of free poison to the level which would just cause a threshold effect in the absence of antidote. This is not Fildes's theory, since he classifies all SH— groups together as an essential metabolite whose absence would itself inhibit growth. The second assumption is therefore that it is necessary to use enough antidote to maintain a threshold concentration of free antidote.

Let m molecules of the poison X combine with n molecules of the antidote Y to form an inactive compound XY , and let x and y be the total molar concentrations of X and Y . Consider the threshold conditions in which there is just enough free X to have an effect. Let the concentration of X which is not combined with Y in these conditions be x_0 , of which x_1 is free and $(x_0 - x_1)$ is combined with the tissue. On the first assumption these quantities are independent of x and y . The concentration of the inactive compound will be $\frac{(x - x_0)}{m}$ molar, and the concentration of free Y will therefore be

$$y = \frac{n}{m}(x - x_0).$$

For equilibrium

$$x_1^{-n} \left[y - \frac{n}{m}(x - x_0) \right]^n = K \frac{(x - x_0)}{m}$$

where K is the dissociation constant of XY .

$$\therefore y = \frac{n}{m}(x - x_0) + \left[\frac{K}{x_1^{-n}} \cdot \frac{x - x_0}{m} \right]^{\frac{1}{n}} \quad . \quad . \quad . \quad (1)$$

The relation may be expressed graphically by plotting y against x (see Fig. 1). The line AE, which expresses conditions giving equal effects is called an isobol.^{11, 12} The straight line AB represents the case where

dissociation is negligible; $K = 0$ and $y = \frac{n}{m}(x - x_0)$. Under these conditions Y is all combined with X and the uncombined X is merely the excess. The last term in equation (1) is represented by ED. This is the extra amount of antidote which must be added to suppress the tendency to dissociation.

¹¹ Fraser, *Brit. Med. J.*, 1872, II, 457, 485.

¹² Loewe, *Ergeb. Physiol.*, 1928, 27, 47.

When $n = 1$, that is when there is only one molecule of antidote in each molecule of the inert compound, AE is a straight line, and the concentration of antidote is directly proportional to the concentration of poison, provided that the latter is corrected by subtracting the amount required in the absence of antidote. When $n = 2$ the curve connecting ED and x is a parabola, and as n becomes longer the relationship diverges more from that of simple proportionality. These statements are true whatever the value of m , which has no effect because x_1 is assumed constant.

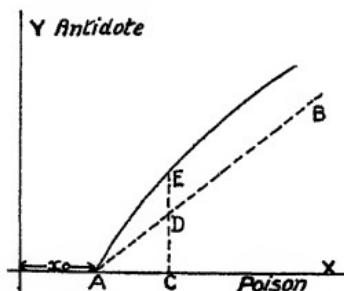


FIG. 1.—AE is the isobol, showing concentrations of poison and a neutralising antidote which have a constant effect. Arithmetic scales.

equation for the theory that the effect depends on the removal of excess antidote can be derived from equation (1) by interchanging x with y and m with n . According to this theory the amount of poison always exceeds the simple chemical equivalent of amount of antidote, corrected as before.

The observations of Voeghtlin and Fildes that a large excess of antidote was sometimes necessary suggest that the second assumption is incorrect in these cases, and that the function of the added SH— compounds is to remove the poison rather than to maintain a threshold concentration of free SH— groups. On the other hand Woods¹³ found that a substance in yeast antagonised sulphanilamide in remarkably low concentrations, and was led to the conclusion that the antagonism was due to competition. There is no doubt that this conclusion was correct, but the above discussion suggests that it was illogical. If K was large, even a small amount of antidote might be sufficient to maintain a threshold concentration of free antidote. A large excess of antidote will only be needed if it is necessary to keep down the concentration of free poison.

This method of calculation is only useful when the total amounts of poison and antidote are known and the amounts free cannot be independently estimated. When this can be done it should be possible to show by direct measurement that the concentration of free poison, or of free antidote, remains constant.

Another important class of antidotes which act by combining with poisons includes the antibodies which appear in the serum of immunised animals. The quantitative aspects of this combination have been discussed by Marrack.¹⁴ There are, of course, other examples.

The general conclusion is that the study of neutralising antidotes is unlikely to lead to new pharmacological knowledge, since they only act by reducing the concentration of free poison, and give no information about the action of the poison different from that obtained by reducing the concentration in other ways.

¹³ Woods, *Brit. J. Exp. Path.*, 1940, 21, 74.

¹⁴ Marrack, 1939. *The Chemistry of Antigens and Antibodies*, M.R.C. Spec. Rep. Ser. No. 230.

Antagonism by Competition.

It is more profitable and interesting to study the drugs which antagonise one another by competition, since it is possible in this way to find out something about the groups for which they compete. A study of competitive antagonisms also leads to a convenient classification of drugs, since those drugs which have the same antagonists probably act on the same receptors. The word receptors is used here to denote the site of action of the drug and does not imply any theory of its nature.

When a drug has combined with the appropriate receptors in a tissue it may either produce a pharmacological response or it may do nothing but block up the receptors and so exclude active drugs.

This process of competition has been attracting attention in many ways. It has long been known to students of enzymes.¹⁵ Hydrogen ions may compete with enzyme poisons, such heavy metals¹⁶ or basic dyes,¹⁷ and hydroxyl ions may compete with acid dyes. Substances allied to the normal substrates of enzymes may also cause competitive inhibition. The pharmacological importance of competition was emphasised by evidence that the actions of eserine were due to the accumulation of acetylcholine preserved by competition from destruction by cholinesterase¹⁸ and that the actions of ephedrine were similarly due to the preservation of adrenaline.¹⁹ Much work has been done on the antagonism between pairs of drugs, such as atropine and acetylcholine, or ergotoxine and adrenaline, which compete for the pharmacological receptors near nerve endings.²⁰

The evidence obtained by Woods,²¹ working in Fildes's laboratory, that the action of sulphanilamide is due to competition between the drug and *p*-amino-benzoic acid has attracted widespread attention and been generally accepted. It led to the discovery that *p*-aminobenzoic acid is a growth factor for certain micro-organisms,²² and also mammals: it has, for example, been found to prevent grey hair in rats fed on a deficient diet,²³ and in cats poisoned with hydroquinone.²⁴ Dr. McIlwain has given us an able review of the developments in this field, including his own striking results, obtained after Dr. Fildes, and other members of the team, became engaged on work in connection with the war.

The Combination of Drug and Tissue.

Dr. Ing²⁵ has given us an interesting account of the ways in which molecules have been stripped of unnecessary coverings revealing the essential skeleton of what he calls pharmacodynamic groups. These groups are sometimes present both in poisons and in their antidotes and are therefore probably important for the combination of the drug with the appropriate receptors, rather than for its subsequent effect. It is possible that they represent the part of the drug which combines with the receptors by means of true valencies.

Many drugs are bases and there is some evidence that tissues can remove such drugs from solutions by a process of base-exchange such as occurs with permuntit.²⁶ In some cases there are two or more groups which probably combine by true valencies and the distance of these apart may

¹⁵ Haldane, *Enzymes* (Longmans Green, 1930).

¹⁶ Myrbäck, *Z. physiol. Chem.*, 1926, 158, 160.

¹⁷ Quastel and Yates, *Enzymologia*, 1936, 1, 60.

¹⁸ Stedman and Stedman, *Biochem. J.*, 1931, 25, 1147.

¹⁹ Gaddum and Kwiatkowski, *J. Physiol.*, 1938-39, 94, 87.

²⁰ Rubbo and Gillespie, *Nature*, 1940, 146, 838.

²¹ Ansbacher, *Science*, 1941, 93, 164.

²² Martin and Ansbacher, *J. Biol. Chem.*, 1941, 128, 441.

²³ Zipf, *Arch. exp. Path. Pharmak.*, 1927, 124, 259.

be critical. The very specific effects of low concentrations of some drugs must depend on a very elaborate fit of the key in the lock, which I suppose depends on polar effects and on the shape of the rest of the molecule. When the fit is good enough, the receptors become saturated in the presence of particularly low concentrations of the drug which is then said to be very active.

On the other hand I do not agree with the view that the activity of a drug probably depends on the ease with which it can combine with receptors. The competition which has been most accurately studied is the competition between oxygen and carbon monoxide for haemoglobin. Both gases combine with haemoglobin in exactly the same way and their dissociation curves are identical, except that the dissociation constant for O_2 is about 240 times that for CO. This constant represents a balance of the opposing processes by which the gases combine with haemoglobin and dissociate again. Roughton²⁴ has shown that both combination and dissociation are slower for CO than for O_2 , but that the dominating factor is the high stability of carboxyhaemoglobin. Owing to this stability, CO is about 240 times as active a drug as O_2 . It seems to me likely that most highly active and specific drugs are also active because they form stable compounds with the tissues. An elaborate fitting together of molecules is clearly necessary and this is more likely to lead to stable combination than to rapid combination.

Dr. Ing's views on optical isomers are interesting. If he is right it might be possible to demonstrate that perfused tissues remove the active isomer selectively from the perfusion fluid.

Quantitative Theory of Competition.

A simple theory accounts for the quantitative facts of competition in many cases.²⁵ Let C_1 be the concentration of free active drug, or essential metabolite, or antidote, and let C_2 be the concentration of free poison competing for the receptors. Let a and b be the corresponding proportions of the receptors occupied by the two drugs, so that $(1 - a - b)$ is the proportion of the receptors free. Then for equilibrium

$$K_1 C_1 (1 - a - b) = a \quad \text{and} \quad K_2 C_2 (1 - a - b) = b.$$

Elimination of b gives

$$K_1 C_1 = (1 + K_2 C_2) \frac{a}{1 - a}. \quad \dots \quad (2)$$

When $C_2 = 0$ this reduces to a mass law equilibrium in its simplest form and has been used to express the uptake of oxygen by haemoglobin, poisons or substrates by enzymes, and acetylcholine and adrenaline by pharmacological receptors. It is identical with the formula used by Langmuir²⁶ to express the adsorption of gases.²⁷ When plotted on an arithmetic scale of concentration it gives a hyperbola, and when plotted on a logarithmic scale it gives the symmetrical sigmoid curve, which is well known as the titration curve of a buffer. This logarithmic method of plotting is convenient because it shows the relation of the simplest curves to those that are less simple.

In the presence of a small amount of acid the curve connecting the concentration of oxygen and the percentage saturation becomes concave at low concentrations, but the curve obtained by plotting the logarithm of the concentration retains its symmetry and only becomes steeper than before. The results can be expressed with fair accuracy by replacing $\log C$

²⁴ Roughton, *Proc. Roy. Soc. B.*, 1934, 115, 451.

²⁵ Gaddum, *J. Physiol.*, 1937, 89, 7P.

²⁶ Langmuir, *J. Amer. Chem. Soc.*, 1918, 40, 1361.

²⁷ Hitchcock, *ibid.*, 1926, 48, 2870.

by $n \log C$, or C by C^n where $n = 2.5$ (Hill²⁸). This suggests a reaction of the second or third order, and it was thought at one time that haemoglobin must be in aggregates each of which could combine with n molecules of oxygen. On this theory it is assumed that an aggregate cannot combine with a single molecule of oxygen, or if it does the compound so formed dissociates so rapidly as to make no significant contribution to the oxygen uptake. It was then shown, by observations of osmotic pressure and with the ultracentrifuge, that haemoglobin dissolves in aggregates each of which could combine with 4 molecules of oxygen, so that n should be 4. This was explained by Adair²⁹ on the theory that each aggregate can combine with anything up to 4 molecules of oxygen and that the stability of the combination increases as the number of molecules of oxygen in each aggregate increases. This theory resembles Hill's in suggesting that unsaturated aggregates are relatively unstable; it suggests that $n < 4$ because their stability is not negligible.

The application of formula (2) to the antagonism of drugs on the receptors at nerve endings has been studied in great detail.¹ The relation between the concentration (C_1) of adrenaline or acetylcholine and their effects on a wide range of tissues is well expressed by this formula, if it is assumed that the effect is proportional to a . When the effect is plotted against the logarithm of the concentration of antidote the curve is the same shape and slope, either in the presence, or in the absence, of antagonistic drugs. The effect of the latter is merely to move the curve horizontally without changing its shape. This is explained on the theory that the reaction between these active drugs and the receptors is always of the first order and that the pharmacological effect is directly proportional to the amount of drug combining with the receptors. On the other hand the combination between antagonists, such as ergotoxine and atropine, with the receptors is not so simple and the results can only be expressed by a formula of the form

$$K_1 C_1 = [1 + (K_2 C_2)^n] \frac{a}{1 - a}. \quad (3)$$

In this formula K_2 represents the reciprocal of the concentration causing a doubling of C_1 . The interaction of heavy metals and dyes and hydrogen ions are expressed by the same formulae.¹

The quantitative aspects of the antagonism of sulphanilamide and *p*-aminobenzoic acid were discussed by Wyss,³⁰ who arrived at an equation identical with equation (2) above, though with a different notation. He pointed out that the rate of growth should depend on a , and that his results indicated that the rate of growth in the exponential phase was directly proportional to a . According to Davis and Hinshelwood³¹ the matter is more complicated than Wyss supposed, since there may be two exponential phases of growth in the presence of sulphanilamide, and growth never stops completely even in high concentrations of sulphanilamide.

The data given by Wyss for the effect of C_2 do not fit formula (2), but do fit formula (3) if $n = 2$. The results of Strauss *et al.*³² appear to support this conclusion, since their results may be fitted by straight lines of slope 2, when $\log C_1$ is replotted against $\log C_2$. These data suggest that C_1/C_2 is not constant. On the other hand Wood³³ found that C_1/C_2 was constant and his data suggest that $n = 1$. Similar variations in n occur in experiments with ergotoxine and adrenaline, or with atropine and acetylcholine.¹ They may perhaps be due to reactions of order different from 1, or to the fact that the concentration of the drugs at their

²⁸ Hill, *J. Physiol.*, 1910, 40, 4P.

²⁹ Adair, *J. Biol. Chem.*, 1925, 63, 529.

³⁰ Wyss, *Proc. Soc. exp. Biol.*, 1941, 48, 122.

³¹ Strauss, Lowell and Finland, *J. Clin. Invest.*, 1941, 20, 189.

³² Wood, *J. exp. Med.*, 1941, 75, 369.

site of action is not directly proportional to their concentration in the liquids in contact with the tissue or to failure to correct for the threshold concentration.

Comparison of Formulae for Neutralisation and Competition.

In comparing formula (3) with formula (1) it must be remembered that C_1 and C_2 represent concentrations of free drug, and x and y represent total concentrations. In experiments on competition it is sometimes possible, by maintaining a large excess of fluid in contact with the tissue, to ensure that the final free concentration is practically equal to the total concentration, but this is not always the case. Some of the variations in the value of n , discussed in the last paragraph, may be due to the assumption that C_1 and C_2 are equal to the total concentrations of the drugs. In any case it is clear that the relationships are similar in the two cases.

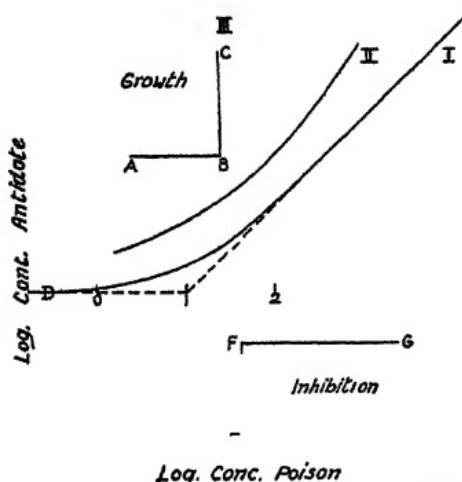


FIG. 2.—Different types of isobol separating conditions for growth (top left) from those for inhibition (bottom right). Logarithmic scales to base 10.

- ABC. No evidence of specific antagonism.
- D. Direct neutralisation or competition. Equations of first order. On arithmetic scales this would be linear.
- EFG. Poison inhibits synthesis of an essential metabolite (the antidote).

by synthesis from indole. Indoleacrylate inhibits growth and the evidence suggests that it competes with a hypothetical substance intermediate in the synthetic chain between indole and tryptophane. This was shown by the fact that a small amount of tryptophane completely antagonised the inhibition, and the amount required was practically unaffected when the amount of indoleacrylate was increased 5 times (FG, Fig. 2). There was no evidence in these experiments that indole had any antagonistic action at all (ABC), but it might be expected that a more detailed analysis would reveal a certain amount of graded antagonism over a small range of low concentrations. Neither substance showed graded antagonism over a wide range of concentrations such as occurs with direct competition

two cases. When the reactions are of the first order the ratio of the concentrations is constant in either case, provided that a correction is made for the threshold concentration of one of the drugs. In neither case is there any theoretical limit to the value of this ratio. It would probably not be possible to distinguish between the two types of antagonism by studying the quantitative relationships, and this can only be determined from independent evidence that the drugs combine with one another, or would be likely to compete.

Other Types of Antagonism.

Fildes ²² has also drawn attention to other interesting types of relation between poison and antidote. Tryptophane is essential for the growth of bacteria, which normally obtain it

(curve D) and would presumably be given by the hypothetical intermediate substance.

In this type of diagram, graded antagonism is shown by a sloping isobol. With linear scales and reactions of the first order, the isobol is straight. Owing to the wide ranges of concentrations involved it is often necessary to use logarithmic scales. If the reaction is of the first order the isobol is then as shown in curve D (Fig. 2) with a slope of 45° . If the isobol becomes parallel to one of the axes at high concentrations (BC or FG) it suggests that the concentration of the corresponding drug has risen above the threshold value required to produce a maximal effect, such as saturation of an enzyme. If the curve becomes parallel to one of the axes at low concentrations (AB or EF) it suggests that the opposite drug has fallen below a threshold value. If the actions of the two drugs are completely independent a curve such as ABC is expected.

Other examples of antagonism have been studied by McIlwain²⁴ who classifies competition as type I of antagonism, and results like those with indole as type III, and describes an intermediate type II, but says nothing about the type of antagonism shown by tryptophane and indoleac-

The competition of O_2 and CO for Hb shows a curious paradox, since at low concentrations in the presence of acid the addition of one gas may increase the combination of the other with Hb.⁶⁵ In this region, where the dissociation curve is concave upwards, doubling the concentration of either gas, taken alone more than doubles the percentage saturation of the haemoglobin. If, therefore, the two gases are present together in equivalent concentrations the percentage saturation will also be more than doubled, and, since equal quantities of each combines, each increases the uptake of the other.

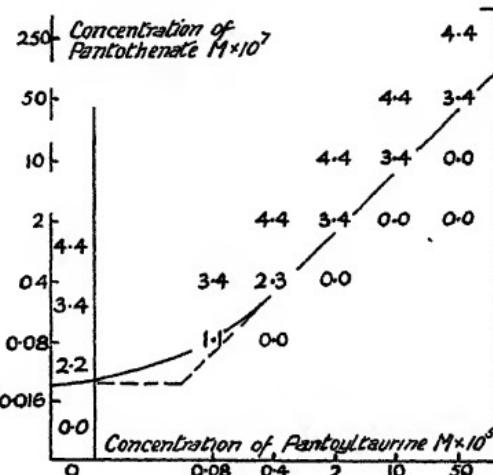


FIG. 3.—A method of tabulating results to show their quantitative relations. The figures denote the growth observed at two different times. Isobols are drawn between the figures to represent any given amount of growth. In this case the antagonism is due to competition (McIlwain's data).

Conclusion-

The high activity and specificity of the action of many drugs depend on the intermolecular forces which bind them to appropriate receptors. As with the narcotics, we know comparatively little about how they really act once they have been concentrated at the site of action. In many

³⁴ McIlwain, *Brit. J. exp. Path.*, 1940, 21, 136; 1941, 22, 148; 1942, 23, 95.

³⁵ Barcroft, *Respiratory Functions of the Blood* (Cambridge University Press, 1928).

cases this is a problem for students of enzymes, and it is to be hoped that they will continue to collaborate with pharmacologists in this field. This collaboration has widened our knowledge both of drugs and of enzymes.

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GENERAL DISCUSSION.

Dr. H. McIlwain (Sheffield) (communicated): I agree with Professor Gaddum that the study of drug-antagonism has proved an extremely valuable means of analysing the effects of drugs. I would like to emphasise an aspect of the subject which is complementary to that discussed by him, and which perhaps alters the balance of his conclusion (on p. 327) that the antagonism of drugs by neutralisation is a less profitable or interesting study than their antagonism by competition. The aspect in question is the natural occurrence of antagonistic substances. Thus, the finding that a particular type of compound is the most potent antagonist which can be extracted from the biological system affected, or from other natural sources, has an important bearing on the mode of action of the drug whether that be by neutralisation or by competition.⁵⁶ In both cases the compound isolated has dual significance: its relation to the drug and to natural processes taking place independently of the drug. It is then a useful working hypothesis to assume that the processes affected by the drug are related to ones in which the antagonist, isolated from natural sources, takes part. Such studies have suggested acriflavine to act by combination with nucleotides,⁵⁷ and mercuric salts by combination with sulphur-containing proteins.⁵⁸ Without such analysis of natural systems, the selection of compounds for testing as antagonists is arbitrary, and those acting by neutralising may well have little significance. This was illustrated⁵⁹ by considering the systems which might be affected by hydrochloric acid, whose antagonism by sodium hydroxide has little biological significance, while its antagonism by natural buffers and basic groups, has such significance.

In investigating natural materials as drug-antagonists one must consider a wider array of modes of interaction than those selected by Professor Gaddum or enumerated in an earlier paper.⁵⁹ Four modes examined recently⁶⁰ in such a study were the following: (1) Reactions between inhibitor and antagonist in the absence of the biological system. (2) Reactions in the presence of the biological system. These two may include the combination referred to by Professor Gaddum, but can occur through types of reaction between inhibitor and antagonist, other than their combination; for example, inactivation of an inhibitor occurred through its reduction in the presence of the biological system together with antagonists, which probably functioned as hydrogen carriers. (3) Neutralisation of effects, but not necessarily chemical reaction between the two components, through independent actions on the biological system; for example, the antagonism of substances inhibiting bacterial growth, by others which independently promote it. (4) Neutralisation, but not chemical reaction between the two components, through related actions on the biological system. This would include such examples as the antagonism by methionine of the antibacterial action of sulphanilamide, as well as its antagonism

⁵⁶ McIlwain, *Lancet*, 1942, i, 412.

⁵⁷ McIlwain, *Biochem. J.*, 1941, 35, 1311.

⁵⁸ Smith, Czarnetzky and Mudd, *Amer. J. Med. Sci.*, 1936, 192, 790.

⁵⁹ McIlwain, *Brit. J. exp. Path.*, 1940, 21, 136.

⁶⁰ McIlwain, *Biochem. J.*, 1943, 37, 265.

by *p*-amino-benzoate. The four modes of interaction are placed in order of increasing specificity of interaction with the biological system and clearly admit of intermediate cases.

I find very valuable Professor Gaddum's tabular representation of the interaction of drug and antagonist (*cf.* ⁴⁰), and am certainly in agreement in recognising the distinctive character of the interaction of indoleacrylate with tryptophan. This (then unpublished) was not included with other types enumerated in 1940,⁴¹ as that analysis was of specific experimental results, but an analogous interaction is discussed later,⁴² and discriminated from other cases. The types⁴³ were characterised by certain quantitative relations, and overlap with the above classification in terms of relationship to the biological component.

⁴¹ Kohn and Harris, *J. Pharm. exp. Ther.*, 1943, 77, 1.

⁴² McIlwain, *Biochem. J.*, 1942, 417

THE CELL METABOLISM OF THE MALARIA PARASITE IN RELATION TO THE MODE OF ACTION OF ANTIMALARIAL DRUGS.

By S. R. CHRISTOPHERS.

Received 9th August, 1943.

In our investigation of the mode of action of antimalarial drugs it seemed probable to Dr. Fulton and myself that antimalarials of the quinine type might function through the inhibition of the enzymes responsible for the cell metabolism of the parasite. We therefore took up the study of this question. We were in a good position to do so since we had been dealing for some time with parasite material as obtained from *Macacus rhesus* monkeys heavily infected with *Plasmodium knowlesi*.

Since we obtained interesting and suggestive results,^{1, 2} and others, especially Coggshall and Maier,^{3, 4, 5} Velick⁶ and more recently Wendel⁷ have confirmed and extended these results, a brief summary of and comment on this line of work seems desirable.

The material mainly employed has been that obtained from *Macacus rhesus* heavily infected with *P. knowlesi*. But other monkey parasites, *P. inui* and *P. cynomolgi*, as also the bird parasites, *P. cathemerium* and *P. lophurae* have been studied in this connection by some authors. Such material may be either the centrifugally separated and washed large forms of the parasite suspended in a suitable medium, or, as originally pointed out by us,¹ whole blood will give satisfactory readings. When whole blood, defibrinated or heparinised, is used, all the elements of the blood including non-parasitised cells are present and the readings show difference between infected and normal blood. In the separated parasites obtained by centrifuging, remnants of the red cell surrounding the parasites are still present amounting usually to about one quarter of the material. Parasites completely free from red cell and apparently but little damaged can, however, be obtained, as shown by Fulton and myself,⁸ through

¹ Christophers and Fulton, *Ann. Trop. Med. and Par.*, 1938, 32, 43.

² Fulton and Christophers, *ibid.*, 77.

³ Coggshall, *J. Exper. Med.*, 1940, 71, 13.

⁴ Coggshall and Maier, *J. Inf. Dis.*, 1941, 69, 108.

⁵ Maier and Coggshall, *ibid.*, 87.

⁶ Velick, *Amer. J. Hyg.*, 1942, 35, 152.

⁷ Wendel, *J. Biol. Chem.*, 1943, 148, 21.

⁸ Christophers and Fulton, *Ann. Trop. Med. and Par.*, 1939, 33, 161.

saponisation of the deposit. In all these forms of material O_2 uptake can be demonstrated and measured.

The method used for determining O_2 uptake has been by the Barcroft differential manometer, usually under aerobic conditions at 37° C.

It has been established up to date that

(1) Suspensions of parasitised cell deposit, or heavily infected whole blood, consumes O_2 at a rate very much greater than that which could arise from either the red cell substance or plasma present. Wendel⁷ notes that parasitised cells in one specimen consumed O_2 about 300 times as rapidly during the first measured period as do cells in normal blood.

(2) Uptake occurs with only a moderate reduction using washed saponised material containing no other elements than the parasites, provided glucose be present.

(3) Uptake is proportional to the amount of parasite deposit or the number of parasites in a given stage of development.

(4) Uptake is much greater with the larger forms of the parasite than with the young stage. Velick⁸ working with *P. cathemerium* found uptake with heavily infected whole blood up to ten times greater in the later stages of the developmental cycle than at its commencement when the parasites were small.

(5) Uptake can be inhibited by even minute traces of certain drugs.

There would seem to be no reasonable doubt but that the very considerable O_2 uptake is due to respiratory metabolism of the parasite.

Changes associated with respiration by trypanosomes have been investigated by a number of observers following upon the pioneer observations on glucose and oxygen consumption by Nauss and Yorke.⁹ O_2 uptake by these organisms has been investigated by Fenyvesy and Reiner,^{10, 11} Kudicke and Evers,¹² Reiner, Smythe and Pedlow,¹³ and Christophers and Fulton.¹ It will be sufficient for our purpose to give the main facts that have been established. A suspension of trypanosomes put up under similar conditions to those employed for the malaria parasites shows an enormous O_2 uptake. With a strain of *T. rhodesiense* Dr. Fulton and myself found an O_2 uptake during the first half hour at the rate of 19.4 ml. per hour for 10^{10} trypanosomes or determined on dried weight $Q_{O_2} = 285$. If no glucose is added to the suspension this rate rapidly falls off and in quarter to half an hour from the using up of such glucose as may have been present in the serum, i.e., in about half an hour's time, all uptake ceases. Even if a considerable amount of glucose be added, say 0.2 per cent., uptake after an hour or so falls and rapidly comes to an end as this amount is exhausted. During this process in which glucose is used up acid is formed. We found just under 1 molecule of glucose (0.9) used up and 2 molecules of monobasic acid formed for each molecule of O_2 taken up. CO_2 is formed but in small amount, the respiratory quotient for *T. rhodesiense* found by us being 0.155. These results are closely parallel to those previously given by Reiner, Smythe and Pedlow¹³ for *T. equiperdum*. These authors found the chief products obtained to be glycerol anaerobically and pyruvic acid aerobically. The respiratory quotient was again small, viz., 0.062, though for *T. lewisi*, a different type of trypanosome, it was approximately 1.0.

Coming to observations on the malaria parasite O_2 uptake is likewise very considerable. Dr. Fulton and myself found it to be in the first half hour at the rate of 2.17 ml. per 10^{10} parasites per hour, or 8.9 times smaller than that for an equal number of trypanosomes, which, however, parasite for parasite would be considerably larger. Q_{O_2} based on dried substance

⁷ Nauss and Yorke, *Ann. Trop. Med. and Par.*, 1911, 5, 199.

¹⁰ Fenyvesy and Reiner, *Z. Hyg.*, 1924, 102, 109.

¹¹ Fenyvesy and Reiner, *Biochem. Z.*, 1928, 202, 75.

¹² Kudicke and Evers, *Z. Hyg.*, 1924, 101, 317.

¹³ Reiner, Smythe and Pedlow, *J. Biol. Chem.*, 1936, 113, 75.

as determined after saponisation was 35, again about 8 times smaller than that for trypanosomes. Nevertheless, though considerably smaller than that for trypanosomes, O_2 uptake for malaria parasite substance is relatively quite large as compared with figures given by different observers for tissue determinations. Our figure of $QO_2 = 35$ was the mean of a large number of experiments using full grown or nearly full grown parasites. Wendel⁷ working with parasites in different stages of development found O_2 consumption in 35 samples to vary between 157 and 2280 ml. per 10^{14} cells per hour, uptake being greatest with the large presegmenter forms. Velick⁸ using whole blood with *P. cathemerium* found at the stage of maximum development of the parasite cycle a difference up to 10 times the uptake when the parasites were small.

A curious feature of O_2 uptake by parasites, and in marked contrast to that by trypanosomes, is that uptake continues apparently indefinitely whether extra glucose has been added or not. There is never the rapid fall off due to exhaustion of the glucose seen in trypanosome material. Indeed this steady uptake continued for many hours (as much in our experience as 10 hours on one occasion) is a very characteristic feature of O_2 uptake by parasites. Nevertheless glucose when present is utilised.

That the continued uptake is merely due to there being sufficient glucose normally present in the serum or red cells does not seem to be the explanation. Wendel says "glucose initially present in a sample of moderately or highly parasitised blood is destroyed during the first hour of incubation *in vitro*, yet at such time *P. knowlesi* may continue respiration at a constant or even accelerated rate." It is not due to glycolysis by normal blood, as this author found, as we did, that the blood of normal monkeys and normal red cells from infected monkeys destroys glucose quite slowly. According to Wendel 10^{14} normal cells destroys glucose at an average rate of 20 mg. per hour at 37° C., whereas parasitised cells destroy it from 5 to 70 times as rapidly. He also found this rate to be increased under anaerobic conditions but not with normal red cells.

As to the amount of glucose used up, Fulton¹⁴ found this to be at the rate of 2.2 mg. in $\frac{1}{2}$ hours by 800 million parasites. This is equivalent to 18.4 mg. by 10^{10} parasites per hour or, reducing to molecular proportions, 1.02 mols. of glucose to 0.98 mols. of O_2 , taking the figure for O_2 uptake we have previously given. It would therefore appear that, as with trypanosomes, the amount of glucose used up as compared to O_2 uptake is approximately unity.

Dr. Fulton and myself were unable to demonstrate by pH determinations that acid was formed in any appreciable amount. More recently Wendel⁷ working with *P. knowlesi* found that if 400-500 mg. glucose be added to the suspension the pH falls progressively until all glucose is destroyed or until pH 5.5 is reached at which point respiration and glycolysis ceased. This author found approximately half of the destroyed glucose to be converted to lactic acid, the remainder being only partially oxidised.

Of a large number of sugars tested by Fulton with *P. knowlesi* only levulose, maltose and mannose were found capable of giving an increase in O_2 uptake, but glycerol was utilised. A similar result in the main was obtained by Maier and Coggeshall.⁹ They found succinate, fumarate, malate and citrate were not utilised, but fructose, mannose, as also glycerol and lactate were. Wendel⁷ believed from his experiments that respiration was only indirectly dependent upon glycolysis, but was due to lactate metabolism.

The respiratory quotient for *P. knowlesi* was found by Christophers and Fulton¹ to approach unity (0.86). Velick⁸ working with *P. cathemerium* obtained figures for the respiratory quotient in 9 birds varying between 0.61 and 0.94, the mean being 0.78. There is thus a marked

¹⁴ Fulton, *Ann. Trop. Med. and Par.*, 1939, 33, 217.

contrast in this respect to the trypanosomes *T. rhodesiense* and *T. equiperdum* where the quotient is in both cases under 0·2.

Time does not permit of these metabolic processes being discussed in further detail. In the main both in trypanosomes and malaria parasites the chief features are the utilisation of glucose, the taking up of oxygen and the formation of acid. But there are evidently some differences. These are even more strikingly apparent when one comes to consider the fundamental enzymic processes involved. Unfortunately these have as yet been very inadequately investigated.

We know that in the case of trypanosomes methylene blue is actively reduced in the Thunberg tube and presumably a hydrogenase system is involved. But the nature of the oxidising part of the system is as yet entirely unknown. Respiration is not inhibited by cyanide as is markedly the case with the malaria parasite showing that there is a different mechanism involved. In the case of trypanosomes deprivation from glucose for as short a period as 15 minutes completely does away with the power to restart O₂ uptake when glucose is later added. Very possibly this is due to the fact that deprivation of glucose leads to rapid lysis of the organisms. It is of interest in such experiments to see that deprivation of glucose has all the appearances of addition of some powerful toxic drug.

The malaria parasite probably also works through a hydrogenase system, but this so far has not been demonstrated owing to the fact that the presence of red cell itself reduces methylene blue in the Thunberg tube and attempts to investigate this point further have not been made. O₂ uptake by *P. knowlesi* is immediately and strongly inhibited by cyanide. Velick¹⁵ working with *P. cathemerium* also found O₂ uptake to be completely inhibited by cyanide, and considers that it is likely therefore that the final stages of the biological oxidations in the parasite are catalysed by the cytochrome : cytochrome-oxidase system. Velick found demonstration of cytochrome-oxidase activity to be made difficult by the fact that the parasite must first be isolated from a system which itself contains the enzyme. But it was possible to demonstrate an increase in oxidase activity during progress of the developmental cycle. The method employed was the rate of oxidation of *p*-phenylene diamine. Though subject to interference by the presence of red cells the rate was found to augment as the parasite cycle advances, and at full maturity of the parasites it may be more than double the original rate when only young forms of the parasite were present. The activity, however, is not strictly parallel to the increase in O₂ uptake.

Keilin and Hartree¹⁶ have made very clear the mechanism of working of cytochrome oxidase and hydrogenase systems. Hydrogenase specific for succinate leads to a transfer of H₂ provided a suitable source of H₂ is present. If methylene blue is present this is made use of and reduced in the process to the leucobase. Under normal conditions in the cell cytochrome *c* is present and is similarly reduced. But in the presence of indophenol-oxidase, which is specific for the reaction, the cytochrome is reoxidised from the atmosphere, thus acting as a "hydrogen carrier." Interference with any part of the chain would inhibit O₂ uptake. Where, as in some other systems, a co-enzyme or more than one co-enzyme enters into the reaction, any chemical or other destruction or blocking of such will also lead to inhibition of O₂ uptake. Inhibition of cell respiration is closely linked with lethality. We are thus brought to the importance of these enzymic activities in relation to the effects of lethal drugs.

Quinine and many compounds of this general type have long been known as inhibitors of enzyme activity and have been much studied from this point of view by Rona and Bloch¹⁷ and others. It seems not at all improbable in view of this property that quinine and other antimalarial

¹⁵ Keilin and Hartree, *Proc. Roy. Soc. B.*, 1937, 122, 298.

¹⁶ Rona and Bloch, *Biochem. Z.*, 1922, 128, 169.

drugs of this general type may exert their effects on the enzymes of the parasite by acting in this way in the body. Added to the experimental flask even in minute amounts such compounds inhibit O_2 uptake by the parasite. They can be tested in this way and depending upon the concentrations at which they act can be given a coefficient of inhibition.³ In their action thus *in vitro* there is often a suggestive relationship to therapeutic effectiveness. Thus among substances tested by Dr. Fulton and myself, quinine, atebrin and plasmoquin all actively inhibit O_2 uptake by *P. knowlesi*, and in much the same proportion as their therapeutic efficiency. A number of sulphonamide compounds have been tested in the same way by Coggeshall and Maier.⁴

That a test of this kind could be used as a short cut to determining the therapeutic effectiveness of different drugs could obviously not be claimed. At the same time it is not unreasonable to suppose that a direct effect *in vitro* of this kind may actually be an indication of the mode of action therapeutically. Also an absence of effect would appear to exclude action of a direct kind in the body. A good example of the latter is the contrast of the *in vitro* effect of pentavalent arsenical compounds on trypanosomes with that exerted in the body. It is generally agreed that these compounds are active therapeutically only because in the body they become changed slowly to the trivalent form. In conformity with this conclusion is the fact that whilst the pentavalent compounds do not act as inhibitors *in vitro*, the trivalent compounds are very powerfully inhibitive. Again Coggeshall and Maier⁴ found sulphanilamide, sodium sulphathiazole and sodium sulphapyridine active *in vitro* in inhibiting O_2 uptake by *P. knowlesi*. "Prontosil" and sulphadiazine were found inactive. The latter is extremely insoluble. "Prontosil" is believed to be effective therapeutically only because it is split up in the body.

It is not, however, as a test, or short cut to looking for new effective compounds that investigation on these lines has its greatest interest or value. Could we determine what particular link in the cell respiratory mechanism was broken by a particular type of inhibitor and why, we should be in a much better position than we are at present to collaborate with the chemist in the synthesis of new compounds, assuming that it is actually in this way that antimalarial drugs act in the body.

It is improbable that every type of drug showing activity against the parasite acts in the same way, but among those which it may reasonably be supposed may act by being enzyme inhibitors are quinine and the other cinchona alkaloids, various derivatives more or less on the quinine model, compounds of the plasmoquin type, compounds related to atebrin and probably some less well known synthetic compounds with the same general chemical structure. The most outstanding feature of all these is that they are complex organic bases. Basic characters would seem in fact to be essential if substances of this type are to be effective in either role. Substitution of groups which eliminate the basic groups in the quinine molecule produces compounds inert against malaria. Schulemann¹⁷ speaking of the search for a synthetic antimalarial compound which led to the discovery of plasmoquin said that until a basic component was included in the molecule no success was achieved. It seems not impossible that their basic make up is responsible for the effect of these compounds upon cell metabolism and possibly for their antimalarial activity.

But their basic make-up is comprised in their *pH* constants. These, along with solubility, determine almost all the reactions of any given base in the test tube, decide the extent to which it will act as a base at any given *pH*, control the proportions of free alkaloid and salts under any given conditions, fix the *pH* of its solutions, the proportion of monovalent and divalent salts and many other properties. Apart from solubility,

¹⁷ Schulemann, Proc. Roy. Soc. Med., 1932, 25, 897.

and excluding molecular disruption, its pK constants make up almost in entirety its characters as a base. It seems therefore not unlikely that the inhibitor and antimalarial effects of such compounds are not so much a direct result of molecular structure as an indirect effect of this working through their basic make-up. If this be really so it has a very important bearing on the line of approach to synthesis of new antimalarial compounds.

Conclusions.

1. The respiratory metabolism of *P. knowlesi*, *P. inui*, *P. cynomologi*, *P. cathemerium* and *P. lophurae* is characterised by utilisation of glucose, the taking up of O_2 in approximately equal molecular proportion and formation of lactic acid. According to Wendel⁷ the direct substrate is lactate, glucose being utilised only indirectly.
2. The process appears to depend upon a hydrogenase-cytochrome-oxidase system, but has as yet been imperfectly investigated.
3. Conspicuous among agents inhibiting such metabolism are basic alkaloid or alkaloidal-like substances including quinine, plasmoquin and atebrin with other antimalarial compounds of this type. Investigation of such inhibitor effect is important both as an *in vitro* test and in fundamental research upon the mechanism of action of antimalarial drugs.
4. The basic make-up of these compounds expressed by their pK constants may be more concerned in such effects than their actual molecular structure.

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GENERAL DISCUSSION.

Dr. H. R. Ing (Oxford) said : If the important feature of the inhibitory activity of quinine, plasmoquin and atebrin are the pK values of the two basic groups, and if the molecular structure of antimalarials of this type is only important in the sense that it determines these pK values, it follows that any organic molecule containing two basic groups with the right pK values should possess inhibitory activity on the malarial parasites. Such a view would open an enormous field to the organic chemist, but it seems more probable that the pK values constitute limiting factors on molecular structures which on other grounds possess antimalarial properties.

(a) Kolthoff, *Biochem. Z.*, 1925, 162, 289; (b) Christophers, *Ann. Trop. Med.* 1937, 31, 43; (c) *idem.*, *ibid.*, 1940, 34, 1.

It is worth noting in this connection that the apparent pK values of nicotine are closer to those of the quinine alkaloids than those of atebrin and plasmoquin.

Sir Rickard Christophers (Cambridge), in answer to Dr. Ing, said : The idea that if we knew what were suitable pK values for a base the molecular chemist might help in the search for new antimalarial compounds was certainly in my mind. A trial on these lines was certainly worth making. Some of the alkaloids whose basic make-up was suitable might quite well be effective against malaria, but this could never be tried be-

Alkaloid.	pK_1 .	pK_2 .
Quinine (a)	5.97	9.70
Quinine (b)	5.70	9.85
Quinidine (a)	5.43	10.00
Cinchonine (a)	5.85	9.92
Cinchonidine (a)	5.80	10.03
Nicotine (a)	6.16	10.96
Atebrin (b)	3.88	6.47
Plasmoquin (c)	3.93	10.51

cause they were highly poisonous due to other features in their molecular structure.

Prof. J. H. Gaddum (Edinburgh) said : This kind of experiment is apt to give misleading results if it is necessary to use high concentrations of drugs to get an effect. Were the concentrations actually used of the same order as those present in the blood when the drugs are used therapeutically ?

Sir R. Christophers, in reply to Prof. Gaddum, said : The concentrations used in our inhibition experiments were often quite of the order in which drugs might occur in the body. In an experiment lasting a relatively short time, however, higher concentrations might be necessary to give results than might be effective in many hours in the body.

Mr. F. Hawking (Hampstead) said that Sir Rickard Christophers' conception that antimalarials are strongly basic does not conform with the fact that sulphonamides, which have an antimalarial action, are approximately neutral, or faintly acid in solution.

Prof. Gaddum said : This technique seems to offer a good opportunity of finding out more about the mechanism by the study of antagonists. Has any search been made for substances which might antagonise the action of drugs in experiments of this kind on malaria ?

Sir R. Christophers, in reply, said : It is very improbable that all drugs having an effect in malaria work through the same mechanism. I was careful in my paper to speak of drugs of the quinine, atebrin, plasmoquin type. One would expect an arsenical compound or a sulphonamide to work in a different manner.

Dr. H. Hurst (Cambridge) said : One of the chief difficulties in the interpretation of antimalarial toxicological data lies in the lack of precise knowledge as to the actual site of drug interaction in the parasite. The experimental evidence suggests that the drug-receptor groups in the parasite enzyme systems are separated from the external drug phase by a protective cell wall which has a lipo-protein mosaic ultrastructure. In systems of this type, selective drug interaction with the cell wall may obscure more specific interaction with the enzyme system, and this may account for the lack of consistency which is apparent in attempts to correlate the antimalarial activity of a drug with expressions of chemical reactivity involving specific pharmacodynamic groups in the drug molecule and drug-receptor combinations. Theories of drug action involving highly specific drug-enzyme-substrate associations are only valid when the disturbing influence of a selective rate of drug access to the site of action has been evaluated. The decrease in drug reactivity with the elimination of the basic groups in alkaloids such as quinine is consistent with a corresponding decrease in drug mobility along the network of functional lipo-protein interfaces of the cell wall framework. The basic groups of the drug molecules appear to exert a "carrier" action on the drug molecules which involves polar interaction with the protein components of the cell wall associated with selective penetration or perhaps dispersion of this phase. In this way, the accessibility of the pharmacodynamic portion of the drug molecule which brings about inhibition of enzyme activity may be greatly influenced. The possibility also exists, however, that change in the basic portion of the drug molecule may influence to some extent drug reactivity at the ultimate site of action in the parasite. Similar results have been with insecticidal drugs, where reactivity involves a prior penetration through a relatively macroscopic lipo-protein framework of the insect cuticle.

Sir R. Christophers, in reply, said : So far as I am aware, nothing is known regarding the distribution of enzymes in the malaria parasites or the intimate surface structure of these organisms.

THE BLOOD-BRAIN BARRIER AND CEREBRO-SPINAL FLUID, IN RELATION TO THE EFFICACY OF SLEEPING-SICKNESS DRUGS.

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Sleeping sickness, or human trypanosomiasis of Africa, may be regarded as a disease of essentially two stages. In the first the infection is practically limited to the blood and the lymphatic system. After a variable time, during which the tissue-spaces of various organs may or may not be invaded, there follows the second and very serious stage, in which some of the trypanosomes have found their way into the substance of the brain. A drug intended as a remedy for sleeping sickness has therefore a considerably more exacting task to perform in the second than in the first stage of the disease, for the reason that those parasites which have penetrated beyond the blood-stream into intimate relationship with the brain-cells are, in their new situation, relatively sheltered from direct impact with trypanocidal agents circulating in the blood. The drug or its metabolite has now to find its way, or to exercise its influence, beyond the blood-brain barrier. It is accordingly important to understand the nature of this barrier and to define the extent and conditions of its resistance to the passage of trypanocides into the extravascular portions of the brain. These are, however, matters about which much remains yet to be explained, and the field should be a most fruitful one for the combined efforts of biologists, chemists, and physical chemists. I intend here to present some facts and opinions as a basis for discussion and further work on the subject.

Localisation of the Blood-brain Barrier, and its Relationship to the Cerebro-spinal Fluid.

The term "blood-brain barrier" (*barrière hémato-encéphalique*) was introduced by Stern,¹ and its lack of anatomical precision indicates the uncertainty that has existed as to its exact localisation, and also that its functions are probably to be regarded as not being exercised by a single strictly delimited organ or system. In fact Stern suggested that the term might be considered not in a purely anatomical sense, but rather as applicable to the mechanism which exercises a selective control over the passage of substances from blood to brain. It is, however, convenient to follow the practice of subsequent writers who have used the term as much in an anatomical as in a functional connotation. In the drawing (p. 341) I have attempted to show diagrammatically the anatomical relationships of the organs and fluids concerned.

It seems certain that the blood-brain barrier is mainly localised in the walls of the cerebral capillaries (Spatz²; Friedemann^{3, 4}); that is to say the passage of substances from blood to brain-cells presumably occurs, for the greater part, directly from the cerebral capillaries through the capillary endothelium into the intercommunicating perivascular and

¹ Stern, *Schweiz. Arch. Neurol. Psychiat.*, 1921, 8, 215.

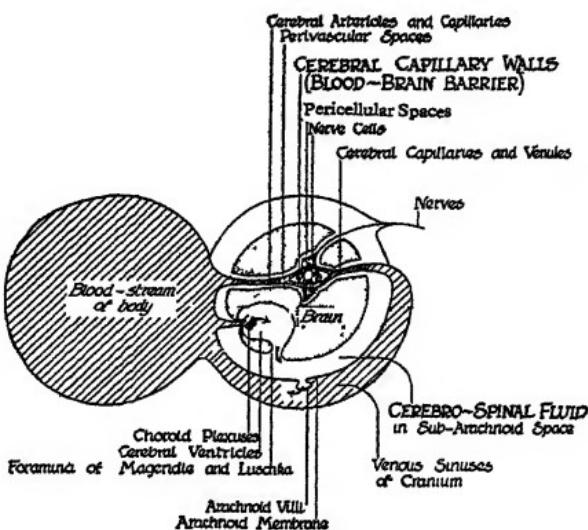
² Spatz, *Arch. f. Psychiat.*, 1933, 101, 267.

³ Friedemann, *Lancet*, 1934, I, 719, 775.

⁴ Friedemann, *Physiol. Rev.*, 1942, 22, 126.

pericellular spaces surrounding the brain-cells. There is little doubt that this view is more tenable than theories (e.g. Stern;⁵ Monakow⁶) criticised by Spatz and by Friedemann, which regard the choroid plexus

Diagram showing relationship of the blood-brain barrier to the cerebro-spinal fluid. Source and circulation of the latter are mainly as indicated by the arrows, but some is believed to be formed also in the perivascular spaces and poured into the subarachnoid space.



or the meningeal vessels as essential parts of the blood-brain barrier, and according to which, therefore, substances finding their way from the blood to the immediate neighbourhood of the brain-cells must necessarily pass through the cerebro-spinal fluid.

The Need of a Technique for determining the Ability of Trypanocides to appear beyond the Blood-brain Barrier.

It is obvious that, in the purposive search in the laboratory for compounds worthy of trial against sleeping-sickness, it would be of very considerable value to have some simple technique which would indicate whether a drug introduced into the blood-stream is capable of appearing, in trypanocidal form, beyond the blood-brain barrier, in the perivascular and pericellular spaces, where it would come into direct contact with trypanosomes in second stage sleeping-sickness. The classical method of selecting potential sleeping-sickness remedies on the basis of their therapeutic effect on the acute septicæmic trypanosome infections of mice clearly does not suffice. This is strikingly illustrated by the case of Antrypol (Bayer 205, Germanin).^{*} In the mouse this compound has an exceptionally high therapeutic index (Haendel and Joetten; Meyer and Zeiss; Wenyon; Yorke, Murgatroyd and Hawking^{7, 8, 9, 10}) far outstripping tryparsamide, yet it has proved considerably inferior to the latter compound in second stage sleeping-sickness. The inadequacy of

⁵ Stern, *Schweiz. Med. Woch.*, 1923, 53, 792.

⁶ v. Monakow, *Schweiz. Arch. Neurol. Psychiat.*, 1921, 8, 233.

* The formulæ of compounds referred to in this paper are given in an Appendix.

⁷ Haendel and Joetten, *Berl. klin. Wschr.*, 1920, 57, 821.

⁸ Mayer and Zeiss, *Arch. Schiffs- u. Tropenhyg.*, 1920, 24, 257.

⁹ Wenyon, *Brit. med. J.*, 1921, 2, 746.

¹⁰ Yorke, Murgatroyd and Hawking, *Ann. trop. Med. Parasit.*, 1931, 25, 313.

tests on infections in mice in the preliminary laboratory evaluation of a drug was well realised by Brown and Pearce¹¹ in their studies on tryparsamide, prior to its actual use against sleeping-sickness. They stressed the importance, in such preliminary work, of making some determination of the drug's power of penetration into the extravascular tissues, and this they considered could suitably be done merely by measuring its therapeutic potency in the chronic infections of rabbits, in which trypanosomes are to be found not only in the blood but also in tissue-spaces in various parts of the body. They found that in mouse infections by *Trypanosoma brucei*, *T. gambiense* and *T. equinum* the therapeutic index of tryparsamide could be described as no more than "fairly good but by no means equal to that of a number of well known substances, such as arsphenamin and neo-arsphenamin, and it is distinctly inferior to that of arsenophenyl-glycine or even arsacetin." However, in well-developed rabbit infections they were satisfied of the superiority of tryparsamide for the reason that, unlike the other arsenicals, it was curative in the same dose per unit bodyweight as for the acute infections of mice. Interpreting this as evidence that the drug possessed a high degree of what they termed "therapeutic penetrability," Brown and Pearce regarded it as the one feature more than any other which justified its trial in naturally occurring trypanosomiasis. However, in spite of the example of tryparsamide, experience has shown that we still cannot gain a sufficient idea of the potential usefulness of a compound in late sleeping-sickness by the mere practice of supplementing tests on the acute mouse septicaemia by further tests on the chronic rabbit infection. This is well shown in the results obtained with drugs which have recently been tested against sleeping-sickness in Africa, namely the arsenical compound Neocryl, and the diamidines, Stilbamidine, Pentamidine and Propamidine. Neocryl had previously been found by Yorke and Murgatroyd¹² to be more effective than tryparsamide in rabbit infections, but it has since proved to be less so in actual late cases of sleeping-sickness (Acres¹³). Similarly the diamidines mentioned were found to be superior to tryparsamide in rabbit infections (Lourie and Yorke¹⁴) but not in late sleeping-sickness (Harding, Bowesman, Lourie, Lawson^{15, 16, 17, 18}).

It is clear that we need a more direct means of deciding whether a drug has the power of appearing in trypanocidal form beyond the blood-brain barrier. The use of dyes, as in the pioneer work of Ehrlich,¹⁹ is of only limited value in this connection. Thus, if the brain-cells are stained after intravenous or subcutaneous injection of a trypanocidal dye, one may indeed infer that the blood-brain barrier is permeable to that particular compound, but no safe assumption may be made on the important question of its concentration in the perivascular and pericellular spaces of the brain. If on the other hand there is no staining of the brain-cells, this does not necessarily mean that the dye has not reached the tissue spaces, for the explanation may simply be that the brain-cells lack an affinity for the dye (King²⁰). In the case of the arsenical drugs in general one may of course estimate the amount of arsenic which lodges in the brain after an intravenous injection, and if this proves to be more than can be accounted for by the blood present in the specimen examined, one may assume that arsenic has passed the barrier (if it has not been

¹¹ Brown and Pearce, *J. Amer. med. Ass.*, 1924, 82, 5.

¹² Yorke and Murgatroyd, *Brit. med. J.*, 1936, I, 1042.

¹³ Acres, *Trans. R. Soc. trop. Med. Hyg.*, 1940, 34, 281.

¹⁴ Lourie and Yorke, *Ann. trop. Med. Parasit.*, 1939, 33, 289.

¹⁵ Harding, *ibid.*, 1940, 34, 101.

¹⁶ Bowesman, *ibid.*, 34, 217.

¹⁷ Lourie, *ibid.*, 1942, 36, 113.

¹⁸ Lawson, *Lowest.*, 1942, 2, 480.

¹⁹ Ehrlich, *Therap. Monatsh.*, 1897, I, 88.

²⁰ King, *Arch. Neurol. Psychiat.*, 1939, 41, 51.

disproportionately adsorbed to the walls of the blood-vessels). But this will give no indication as to whether the form which it has assumed beyond the barrier, in the perivascular and pericellular spaces, is or is not trypanocidal. One would wish, if it were possible, to obtain samples of the fluid in these spaces for tests of trypanocidal activity but it seems to be technically quite an unattainable ideal adequately to tap these microscopical channels.

It has frequently been assumed that the power which a drug possesses of penetrating the blood-brain barrier after introduction into the blood-stream may be judged by its subsequent identification in the cerebro-spinal fluid, *i.e.* that if a compound appears in the cerebro-spinal fluid it must therefore be capable of appearing in the tissue spaces of the brain. This is, however, an unjustifiable assumption, when one considers the commonly accepted theory of the origin and circulation of the cerebro-spinal fluid in the cranial cavity (see diagram). The fluid is believed to be formed mainly by the choroid plexuses in the cerebral ventricles; it then passes through the Foramina of Magendie and Luschka into the subarachnoid space, whence it is absorbed into the blood-stream mainly *via* the arachnoid villi in the cranial venous sinuses. It may be seen that this circuit does not anywhere traverse the brain-tissue, and it follows therefore that if, after administration say intravenously or by mouth, a drug be detected in the cerebro-spinal fluid, this is no reliable indication that it has penetrated the blood-brain barrier, or that it will do so. One must, however, not lose sight of the fact that, although the bulk of the cerebro-spinal fluid is believed, on very good evidence, to be produced by the choroid plexuses, it seems probable that a small quota is also contributed by fluid reaching the subarachnoid space directly from the perivascular spaces of the brain (Weed²¹). While it remains true, therefore, that a compound found in the cerebro-spinal fluid has not necessarily traversed the tissue spaces of the brain, yet it may to some slight extent have done so. There can likewise be no unequivocal interpretation of a failure to detect the compound in the cerebro-spinal fluid. While this might well mean that it had not passed the blood-brain barrier, there does remain the possibility that it may in fact have been in effective concentration in the minute perivascular spaces of the brain, but on reaching the subarachnoid space it may have become so diluted, in the bulk of fluid formed at the choroid plexuses, as to be no longer detectable.

The position seems to them that there is no unexceptionable means at our disposal of directly determining whether a drug has or has not the power of appearing, in trypanocidal form, in the tissue spaces of the brain. Probably our nearest approach to the decision would lie in examination of the cerebro-spinal fluid, although on theoretical grounds this method remains subject to serious doubts and questions. There is, however, the following further consideration in favour of testing the penetrating powers of potential trypanocides into the cerebro-spinal fluid. The simple statement that in second stage sleeping-sickness some of the trypansomes find their way from the blood to the tissue-spaces of the brain does not necessarily imply that they always do so exclusively by direct passage through the capillary walls. Although characteristically they are easily demonstrable in the cerebro-spinal fluid in late sleeping-sickness, there are, in fact, very few recorded observations of trypansomes actually seen in sections of brain, and there is no certainty as to the usual route by which they pass from the blood to the extravascular portions of the brain. They have been found in the latter situations in man by Stevenson,^{22, 23} and in experimental animals by Wolbach and Binger,²⁴

²¹ Weed, *Physiol. Rev.*, 1922, 2, 171.

²² Stevenson, *Trans. R. Soc. trop. Med. Hyg.*, 1922, 16, 135.

²³ Stevenson, *ibid.*, 1923, 16, 384.

²⁴ Wolbach and Binger, *J. med. Res.*, 1912, 27, (New Series 22), 83.

Stevenson,²³ Peruzzi,²⁵ and Hoeppli and Regendanz²⁶ Wolbach and Binger found them to be present in considerable numbers not only in the perivascular spaces and in the perivascular cellular infiltrations typically associated with brain-involvement in trypanosomiasis, but also actually in the walls of small blood vessels and capillaries. This suggests that, as has often been assumed, the trypanosomes do pass directly from blood-capillaries to the perivascular spaces. However, Stevenson, Peruzzi, and Hoeppli and Regendanz found them in masses in the choroid plexuses, and it is likely that in most of the cases of sleeping sickness in which trypanosomes are present in the cerebro-spinal fluid the organisms in this situation derive immediately from the choroid plexus. If this be so, then trypanosomes which invade the brain, in second stage sleeping-sickness, may do so, at least in some cases, *via* the ventricular or subarachnoid cerebro-spinal fluid, rather than directly through the walls of the cerebral capillaries. Quite independently of its powers of penetrating the cerebral capillary walls, therefore, a drug which can attack trypanosomes in the ventricular and subarachnoid spaces should be preferred, on theoretical grounds, to one which acts only within the blood-stream.

Trypanosomes which pass from the cerebro-spinal fluid into the brain substance probably do so by journeying up the perivascular and peri-cellular spaces (see diagram) and no doubt their motile powers would facilitate penetration in what might otherwise be an unlikely direction. The idea that trypanosomes are possibly capable of passing from the circulating blood to the brain *via* the cerebro-spinal fluid raises again the question whether drugs may not, after all, follow a similar route, in accordance with the discredited theories of Stern and Monakow,^{5, 6} mentioned above. In other words, if a compound be shown to have reached the cerebro-spinal fluid from the blood-stream, may we expect it to flow or diffuse into the brain along the perivascular and other similar microscopical channels? It is perhaps reasonable to expect such a diffusion particularly if the concentration of the compound in the cranial venous sinuses be considerably higher than in the cerebro-spinal fluid, as would certainly be the case after the intravenous injection of some drugs. It is generally believed, however, that the actual flow of fluid in the perivascular spaces is normally in the outward direction, towards the surface of the brain. In this connection it is worth mentioning, in passing, that there is evidence (*e.g.* Weed and McKibben; Foley^{27, 28}), that the normal direction of flow in these spaces can be reversed by the osmotic effects of the intravenous injection of strongly hypertonic solutions of sodium chloride. Weed and McKibben describe the process as "the dislocation of a considerable quantity of the cerebro-spinal fluid into the nervous system." In the light of this it might be worth while to explore the therapeutic potentialities of combining treatment by drugs known to be capable of penetrating into the cerebro-spinal fluid with the intravenous injection of strongly hypertonic sodium chloride solutions, in advanced sleeping-sickness.

Examination of Trypanocidal Power of the Cerebro-spinal Fluid after Intravenous Treatment.

The trypanocidal power of cerebro-spinal fluid after intravenous injection of various arsenicals has been tested by Voegtlⁱⁿ *et al.*²⁹ and by

²³ Peruzzi, "Final Report of the League of Nations International Commission on Human Trypanosomiasis," Geneva, 1928.

²⁵ Hoeppli and Regendanz, *Arch. Schiffs- u. Tropenhyg.*, 1930, 34, 1 and 67.

²⁷ Weed and McKibben, *Amer. J. Physiol.*, 1919, 48, 531.

²⁸ Foley, *Arch. Neurol. Psychiat.*, 1921, 5, 744.

²⁹ Voegtlⁱⁿ, Smith, Dyer and Thompson, *Publ. Hlth. Rep.*, 1923, 38, 1003.

Hawking *et al.*^{30, 31, 32} Voegtlin used rabbits, and his method was to trephine the skull and then to inject trypanosomes into the subarachnoid space and the drug into the marginal ear vein. After 24 hours the animal was killed, the trephine opening enlarged, and cerebro-spinal fluid withdrawn and examined for the presence of trypanosomes. Hawking used human subjects, and he tested the trypanocidal power of the cerebro-spinal fluid *in vitro*, according to the technique of Yorke, Adams and Murgatroyd.³³ The method used by Hawking is simpler than that of Voegtlin, but there are obvious difficulties, as well as certain technical disadvantages, in the use of human subjects for large-scale routine preliminary tests of cerebro-spinal fluid activity, in the search for new remedies for sleeping-sickness. With Dr. H. O. J. Collier, in work which is as yet unpublished, I have returned to the use of rabbits, but our technique does not involve the trephining operations which Voegtlin found necessary, and, like Hawking, we estimate the trypanocidal activity of the cerebro-spinal fluid by tests *in vitro*.

Of the compounds examined by Voegtlin and by Hawking and their co-workers, certain pentavalent aromatic arsonates, notably tryparsamide and orsanine were found to render the cerebro-spinal fluid trypanocidal after intravenous injection, while others, such as neocryl, were deficient in this property. These results are in line with the proved therapeutic value of tryparsamide and orsanine, and the ineffectiveness of neocryl in advanced sleeping-sickness. Among the arsenobenzene derivatives, arsphenamine and neoarsphenamine imparted only inconspicuous trypanocidal powers to the cerebro-spinal fluid, but sulpharsphenamine did not fall far short of tryparsamide in this respect. Collier and I have confirmed, in our tests *in vitro*, that tryparsamide renders the cerebro-spinal fluid of rabbits trypanocidal; the trivalent derivative of tryparsamide, reduced tryparsamide thioglycollate, lacks this property. We have also found neoarsphenamine to be far more effective than did Voegtlin and Hawking, in conferring trypanocidal powers on the cerebro-spinal fluid, and this, together with Voegtlin's and Hawking's finding in regard to sulpharsphenamine, mentioned above, suggests that the potentialities of the arsenobenzene derivatives in the chemotherapy of sleeping-sickness have not yet been fully explored.

Factors Determining the Ability of Substances (*a*) to Penetrate the Blood-brain Barrier, and (*b*) to Appear in the Cerebro-spinal Fluid.

The factors which determine ability of compounds to penetrate the blood-brain barrier are not well understood, and the literature on the subject is somewhat confused. Friedemann³⁴ has reviewed the matter, and he states that as far as non-polar substances are concerned there is little doubt that lipid solubility or surface activity play an important part. However, among polar substances (with which we are mainly concerned), Friedemann concludes that molecular size, lipid solubility and diffusibility are only of minor consequence, the important factors being the electro-chemical properties of the substances concerned. He claims that, in the toxins and drugs investigated, ability to penetrate the blood-brain barrier is associated with a positive or no charge at the pH of blood, while inability to penetrate the barrier is associated with a negative charge.

Wittgenstein and Krebs³⁴ studied the penetration of substances from

³⁰ Hawking, Hennelly and Quastel, *J. Pharmacol.*, 1936, 59, 157.

³¹ Hawking, Hennelly and Wales, *ibid.*, 1938, 64, 146.

³² Hawking, *Trans. R. Soc. trop. Med. Hyg.*, 1940, 34, 269.

³³ Yorke, Adams and Murgatroyd, *Ann. trop. Med. Parasit.*, 1929, 23, 501.

³⁴ Wittgenstein and Krebs, *Z. Ges. exp. Med.*, 1926, 49, 553.

blood to cerebro-spinal fluid, and the factors which they found to be associated with this passage are at variance, in several particulars, with those which Friedemann regards as determining penetration of the blood-barrier. Like Friedemann, they attached great significance to electro-chemical properties, but unlike his conclusion in regard to penetration of the blood-brain barrier, their finding was that among diffusible substances it is the negatively charged acid compounds which penetrate into the cerebro-spinal fluid, while the positively charged basic substances fail to do so. Penetration into the cerebro-spinal fluid was also believed to be partly determined by diffusibility, or degree of dispersion, since substances which are of a colloidal nature, even though they carry a negative charge, do not appear in the cerebro-spinal fluid. The conclusions of Wittgenstein and Krebs seem to be broadly in harmony with known facts in regard to the powers of penetration into the cerebro-spinal fluid of drugs effective against trypanosome infections, though it remains for further work to establish the precise extent of this agreement. Thus, tryparsamide, which has the power of penetrating into the cerebro-spinal fluid, is the sodium salt of an acid, and probably circulates in the blood, to some extent at least, as a negatively charged ion. Neoarsphenamine presumably also circulates in the anionic state, and sulpharsphenamine, which is said to penetrate more readily into the cerebro-spinal fluid than neoarsphenamine, is probably still more electronegative in character than that compound, as an effect of its rather strongly acid radicals. The diamidines, which appear to be incapable of reaching the cerebro-spinal fluid, are salts of strong bases and undergo a high degree of ionisation in dilute solution.⁵⁵ Antrypol, which has only slight powers of penetration into the cerebro-spinal fluid, is an acidic compound, presumably circulating in the blood, in part, as an anion, but it has a very large molecule and probably circulates in a semi-colloidal form, or, as believed by Mayer and Zeiss,⁵⁶ bound to plasma proteins.

In attempting to correlate the electro-chemical properties of substances with their powers of penetrating vital membranes, it must be remembered that numerous complicating (or related) factors operate *in vivo*. There are for example different rates of disappearance from the blood-stream, and different rates of excretion. There is also the factor of different degrees of toxicity. In general, electronegative are much less toxic than electropositive substances, and they remain in the circulation for a longer time. Accordingly, since they can be introduced into the circulation in greater amount, and do not disappear as rapidly, they have to that extent a better opportunity of penetrating vital membranes. However, their lower toxicity for the host reflects also, in general, a lower lethality to the trypanosome; mere ability of a negatively charged substance to appear in the cerebro-spinal fluid is valueless for our purpose if unaccompanied by trypanocidal properties. With these considerations in mind the case of drugs of the tryparsamide type is perhaps highly significant. Tryparsamide is relatively non-toxic to the host and has practically no direct trypanocidal action. These features may, according to the foregoing, be considered as related to its electronegative charge, by virtue of which also it gains admission to the cerebro-spinal fluid. It is then reduced to the corresponding trivalent compound, this involving a radical alteration in the charge carried, together with the emergence of a highly trypanocidal property. The effect is, therefore, that a substance (reduced tryparsamide) which is extremely lethal to trypanosomes but which is unable, by its own nature, to penetrate into the cerebro-spinal fluid is nevertheless rendered available for action in that situation.

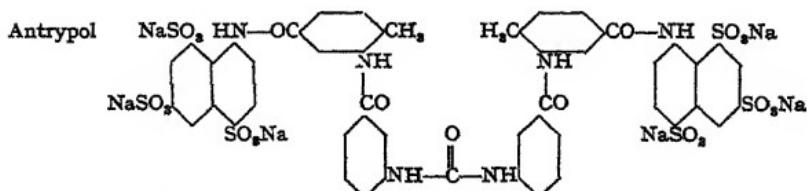
*School of Tropical Medicine,
Pembroke Place, Liverpool 3.*

⁵⁵ Henry and Grindley, *Ann. trop. Med. Parasit.*, 1942, 36, 102.

⁵⁶ Mayer and Zeiss, *Arch. Schiffs- u. Tropenhyg.*, 1921, 25, 259.

APPENDIX.—CHEMICAL FORMULÆ

Tryparsamide	$\text{CONH}_2 \cdot \text{CH}_2 \cdot \text{NH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{AsO} \cdot \text{OH} \cdot \text{ONa}$
Orsanine	$\text{CH}_3\text{CO} \cdot \text{NH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{AsO} \cdot \text{OH} \cdot \text{ONa}$
Neocryl	$\text{CH}_3\text{NH} \cdot \text{CO}(\text{CH}_2)_2\text{CO} \cdot \text{NH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{AsO} \cdot \text{OH} \cdot \text{ONa}$
Reduced tryparsamide thioglycollate	$\text{CONH}_2 \cdot \text{CH}_2 \cdot \text{NH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{As}(\text{S} \cdot \text{CH}_2 \cdot \text{COONa})_2$
Arsphenamine	$\text{OH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{As} = \text{As} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{OH}$
Neoarsphenamine	$\text{OH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{As} = \text{As} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{NH} \cdot \text{CH}_2\text{O} \cdot \text{SO}_3\text{Na}$
Sulpharsphenamine (according to Voegtlin and Johnson ²⁷)	$\text{NaO}_3\text{S} \cdot \text{O} \cdot \text{CH}_2 \cdot \text{NH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{As} = \text{As} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{OH}$ $\text{NH} \cdot \text{CH}_2 \cdot \text{O} \cdot \text{SO}_3\text{Na}$
(according to Dyke and King ²⁸)	sodium salt of $\text{HO} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{As} = \text{As} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{OH}$ $\text{NH} \cdot \text{CH}_2 \cdot \text{O} \cdot \text{SO}_3\text{H}$ $\text{N} \begin{array}{c} \text{CH}_2 \cdot \text{O} \cdot \text{SO}_3\text{H} \\ \\ \text{CH}_2 \end{array}$
Stilbamidine	$\text{NH}_2 \cdot \text{NH} \cdot \text{C} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{CH} : \text{CH} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{C} \cdot \text{NH} \cdot \text{NH}_2$
Pentamidine	$\text{NH}_2 \cdot \text{NH} \cdot \text{C} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{O}(\text{CH}_2)_2\text{O} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{C} \cdot \text{NH} \cdot \text{NH}_2$
Propamidine	$\text{NH}_2 \cdot \text{NH} \cdot \text{C} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{O}(\text{CH}_2)_2\text{O} \begin{array}{c} \text{O} \\ \text{C}_6\text{H}_4 \end{array} \text{C} \cdot \text{NH} \cdot \text{NH}_2$

²⁷ Voegtlin and Johnson, *J. Am. Chem. Soc.*, 1922, 44, 2573.²⁸ Dyke and King, *J. Chem. Soc.*, 1935, 805.

GENERAL DISCUSSION

Dr. E. M. Lourie (*Liverpool*), in introducing his paper, said : Before offering my contribution to this Discussion, I would like to associate myself with the handsome and very fitting tribute which Sir Henry Dale has paid to the memory of Warrington Yorke.

It was my great privilege to know and to work intimately with Yorke for many years until the time of his death. He endeared himself as a wise chief, a generous colleague, and a loyal friend.

He will be sadly missed by many, not only because of his outstanding achievements in the advancement of Science, but also because of the exceptional person that he was.

Dr. H. McIlwain (*Sheffield*) said : Dr. Lourie's communication, in conjunction with my own, emphasises the complexity, both chemical and structural, of the system involved in chemotherapy, and the care which should be exercised before conclusions respecting the mode of action of an agent are drawn from its differing activities under different conditions. It is an indication of the immaturity of chemotherapy that many investigators do not discriminate between the chemical (including biochemical) and structural factors before concluding that one or the other is responsible for variations in chemotherapeutic activity. Thus, activity or inactivity in different hosts may depend upon varying concentrations of antagonists, varying metabolism of the drug or antagonists, varying location of the infection, differences in natural defences, and other circumstances. These have rarely been fully explored, though many opinions have been expressed from partial investigations which in reality are inadequate to show whether an active agent has reached a given site; whether, when reaching it, the agent has been inactivated by antagonists or metabolism; or whether the differences lie in other activities of the parasite and host.

EFFECTS OF NARCOTICS AND BENZEDRINE ON METABOLIC PROCESSES IN THE CENTRAL NERVOUS SYSTEM.

By J. H. QUASTEL.

Received 16th September, 1943.

Narcotics include a large variety of structural types such as hydrocarbons, alcohols, ethers, urethanes, sulphones, amides, etc., and it is evident that their common characteristic of inducing narcosis in animals must depend upon certain physicochemical characters which they have in common rather than upon the possession of any special chemical constitution. The Overton-Meyer theory suggests one important factor in the determination of narcotic activity, i.e., the relative solubilities in the lipid and non-lipoid constituents of the cell or cell surfaces. It is clear, however, that if the non-polar-polar character of a substance determines, or partly determines, its entry into a cell, or its orientation at a surface, it gives no obvious clue to the mechanism of action of the narcotic.

The narcotics as a class are, biochemically, inert molecules undergoing little or no change so far as is known in presence of the living cell. It is reasonable to suppose that their pharmacological activities are directly related to their surface activities.

If it can be shown that the narcotics are associated with a metabolic process in the cell and more particularly with some specific component involved in this process, an advance will have been taken in relating

narcosis to cell chemistry, and in throwing more light on the manner in which narcotics exert their physiological effects.

It has long been known that narcotics as a general rule inhibit enzymic and respiratory processes but until recently there has been reluctance to associate narcosis with a suppression of oxidative events. This has been partly due to the fact that the quantities of narcotics required to induce narcosis in an animal are usually of a far smaller order than those required to inhibit enzymic reactions. Moreover, there has not been until recently any clear evidence that during narcosis in an animal there is a fall in respiratory activity in the nervous system upon which the narcotics might be expected to exert their greatest effects.

McClure *et al.*¹ have, however, demonstrated the existence of anoxia in the central nervous system during the anaesthesia brought about by barbiturates and other narcotics, and according to Shaw *et al.*² ether anaesthesia is associated with a decrease in the difference between the oxygen contents of arterial and venous bloods. Dameshek *et al.*³ have shown that in the human subject under the influence of amytal there is a small but definite inhibition of oxygen uptake and dextrose utilisation by the brain.

Very many facts point to the profound influence of brain oxidations on its functional activity. Moreover it has been clearly established that glucose is the main substrate of the brain in the living animal, and that the oxygen utilised by the brain is mainly concerned with combustion of glucose supplied by the blood (for evidence see⁴). A deprivation of glucose from the brain has as dire physiological effects as a deprivation of oxygen.

Some idea of the vulnerability of the brain to oxygen lack may be gained by the following facts. An interruption of cerebral circulation for 6 to 8 seconds will produce loss of consciousness. The usual action potentials in the cat's cortex are obliterated by a cerebral anaemia of 20 seconds.⁵ Oxygen lack in dogs for longer than 5 minutes results in cessation of cerebral functions.⁶ Unconsciousness will supervene if the oxygen supply to the brain is suddenly reduced to such an extent that oxygen saturation of the blood in the internal jugular vein falls to 24% or less. Consciousness is maintained if the oxygen saturation value is 30% or more.⁷ Brain potentials are abolished in anoxæmia.⁸

In hypoglycæmia due to insulin administration there is a marked change in nature of cortical potentials, and electrical activity may cease if the hypoglycæmia is prolonged.⁹ The frequency of cortical potentials becomes lower with fall of blood sugar and at low levels of blood sugar the waves may disappear.¹⁰ The administration of glucose results in a restoration of the original rhythm after an interval depending on the severity and duration of the preceding hypoglycæmia.

Thus both oxygen and glucose lack lead to a slowing or abolition of cortical potentials. Gibbs *et al.* have now shown¹¹ that the administration of luminal brings about a slowing in the rate of cortical waves.

The physiological facts point to a very high degree of dependence of mental function on the maintenance of oxygen and glucose supply to the

¹ McClure, Hartmann, Schnedorf and Schelling, *Ann. Surg.*, 1939, 110, 836.

² Shaw, Steele and Lamb, *Arch. Surg.*, 1937, 35, 1.

³ Dameshek, Myerson and Loman, *Am. J. Psychiat.*, 1934, 91, 113.

⁴ Quastel, *Physiol. Rev.*, 1939, 19, 135.

⁵ Simpson and Darbyshire, *Amer. J. Physiol.*, 1934, 109, 99.

⁶ Heymans and Bouckaert, *Compt. Rend. Soc. Biol.*, 1935, 119, 324.

⁷ Lennox, Gibbs and Gibbs, *Arch. Neurol. Psychiat.*, 1935, 34, 1001.

⁸ Davis, Davis and Thomson, *Amer. J. Physiol.*, 1938, 123, 51; Hoagland, *ibid.*, 1938, 123, 102.

⁹ Hoagland, Rubin and Cameron, *ibid.*, 1937, 120, 559.

¹⁰ Maddock, Hawkins and Holmes, *ibid.*, 1939,

¹¹ Gibbs, Gibbs, and Lennox, *Tr. Amer. J. Neurol.*, 1937, 63, 129.

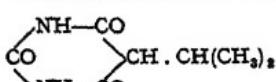
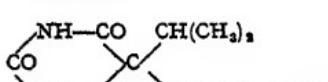
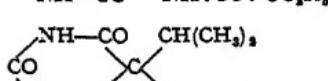
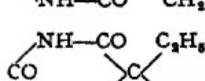
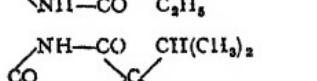
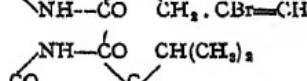
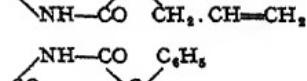
central nervous system. An interference with the respiratory activity of the nervous system by the action of a drug would be expected to disturb its functional activity, the disturbance being proportional to the degree to which the respiratory activity is affected. The action of the drug, hence the fall in respiratory activity, may be highly localised; a large fall, therefore, in the respiration of the entire nervous system by biologically active concentrations of the drug might not be anticipated either *in vivo* or *in vitro*.

Effects of Narcotics on the Respiration of Brain *in vitro*.

Narcotics at low concentrations have the power of inhibiting the respiration of brain tissue whether this be examined in the form of a mince¹² or in the form of thin intact tissue slices.¹³

The effects of seven alkyl barbiturates on the oxygen uptake of minced guineapig brain respiring in the presence of glucose are shown in Table I.¹²

TABLE I.

Barbiturate (0·12 %).	Hypnotic Activity.	% Inhibition of Oxygen uptake of Minced Guineapig Brain in Presence of Glucose.
	○	6
	○	4
	Very weak	○
	+	10
	++	50
	+·-	40
	++	57

The relative hypnotic activities of the drugs are also shown, these being expressed by the symbols: ○ representing lack of activity, + a weak

¹² Quastel and Wheatley, *Proc. Roy. Soc. B*, 1932, 112, 60.

¹³ Jowett and Quastel, *Biochem. J.*, 1937, 31, 565.

activity and + + a relatively high hypnotic action. The following points of interest are worthy of note:

(1) Whereas isopropyl barbiturate is almost inert both as a hypnotic and as an inhibitor of oxidations, the isopropylallyl derivative is very active in both respects.

(2) The combination of isopropyl barbiturate with urethane leads to no appreciable increase in hypnotic or inhibitive powers.

(3) The introduction of a Br atom into allyl radicle of allylisopropyl barbiturate does not affect appreciably the latter's hypnotic or inhibitive effects. The reduction, however, of the unsaturated linkage of the Br derivative to isopropyl-brompropyl barbiturate greatly reduces both hypnotic and inhibitive powers of the drug.

There is a rough parallelism in this series of barbiturates between hypnotic and inhibitive powers.

This parallelism is shown among narcotics of different chemical types. Thus chloral, which is a more powerful narcotic than paraldehyde, has also greater inhibitive effects on brain respiration *in vitro*. The same phenomenon is observable with hyoscine and atropine.

Using the more sensitive brain slice technique in which brain cortex tissue alone is used, it is possible to show^{13, 14} that definite inhibitions of respiration take place in the presence of narcotics at concentrations which produce narcosis in animals. Results in Table II¹⁴ make it clear that

TABLE II.—NARCOTISING CONCENTRATION AND EFFECTS ON THE RESPIRATIONS OF BRAIN CORTEX SLICES IN A GLUCOSE MEDIUM.

Narcotic.	Animal.	Estimated Narcotic Dose g./kg.	Narcotising Concentration (m.).	% Inhibition of Isolated Brain Tissue Respiration due to Narcotising Concentration.
Ethyl urethane . .	Rat	2	0.022	6
Chloral hydrate . .	"	0.22	0.0013	10
Luminal . . .	"	0.2	0.00079	15
Chloretone . . .	"	0.18	0.0010	20
Evipan . . .	Guineapig	0.16	0.00062	17
Avertin . . .	Rat	0.3	0.00106	31
Chloretone . . .	Guineapig	0.18	0.0010	32

a variety of narcotics, at their narcotising concentrations, produces inhibitions of respirations varying from 6 % to 32 %. The results are not inconsistent with the view that the narcotics considered produce approximately equal inhibitions (of the order of 15 %) of the respiration of brain slices when present at concentrations which in the organism would produce an equal fairly deep narcosis. The data, as Jowett states, do not establish this view, but are sufficient to show that a definite inhibition of respiration is produced by concentrations of the order of those producing deep narcosis. The inhibitions recorded represent the effects of the narcotics on the respiration of the entire brain cortex of the animal; they may clearly be much greater at those parts of the nervous system where the narcotic becomes localised.

The action of narcotics on the combustion of all substrates attacked by the brain is not a general one. The oxidations of glucose, lactate and pyruvate are the most affected by narcotics, whilst the oxidations of succinate and *p*-phenylene diamine are undisturbed.^{13, 14}

Results in Table III¹⁴ show these effects, as well as indicating a sensitivity of glutamate oxidation to narcotics. These results were

¹⁴ Jowett, *J. Physiol.*, 1938, 92, 322.

obtained using minced guineapig brain. Data obtained by the more sensitive tissue slice technique are shown in Table IV¹³ where the effects of luminal on rat brain cortex oxidations are recorded.

The high sensitivity of glucose oxidation in brain to the narcotics is a striking feature of narcotic action *in vitro* and, in view of the great im-

TABLE III.—PERCENTAGE INHIBITION BY NARCOTICS (0·12 %) OF OXYGEN UPTAKES OF MINCED GUINEAPIG BRAIN PRODUCED BY VARIOUS SUBSTRATES.

	Allylisopropyl Barbiturate.	Luminal.	Chloretone.	Hyoscine.	Chloral-hydrate.
Glucose . .	73	94	93	79	66
Na Lactate . .	71	79	88	73	90
Na Pyruvate . .	67	85	84	71	90
Na Succinate . .	2	0	0	0	0
Na Glutamate . .	28	50	59	60	62
p-Phenylenediamine	0	0	—	—	—

TABLE IV.—EFFECTS OF LUMINAL (0·08 %) ON BRAIN RESPIRATION IN PRESENCE OF VARIOUS METABOLITES. (RAT BRAIN CORTEX SLICES.)

Metabolite.	Q_{O_2} without Narcotic.	Q_{O_2} with Narcotic.	% Effect of Narcotic on Q_{O_2} .
Nil	2·9	2·75	-5
Glucose 0·01 M. . .	12·2	5·5	-55
Na d. Lactate 0·02 M. .	13·5	8·8	-35
Na Pyruvate 0·02 M. .	11·1	8·1	-27
Na Glutamate 0·02 M. .	8·0	6·8	-15
Na Succinate 0·02 M. .	9·5	10·2	+7

TABLE V.—EFFECT OF 0·033 % EVIPAN * ON RESPIRATION OF GUINEAPIG TISSUES IN PRESENCE OF GLUCOSE.

Tissue.	Respiration (Q_{O_2}).	Respiration (Q_{O_2}) in Presence of Narcotic.	% Inhibition by Narcotic.
Brain . .	14·2	9·5	33
Spleen . .	7·7	6·4	17
Liver . .	4·25	4·15	2
Testis . .	8·65	7·25	16
Kidney . .	15·2	15·95	Nil.

* Na N-methyl cyclo hexenyl methyl barbiturate.

portance of glucose oxidation in the functional activity of the central nervous system (see also¹⁴), this sensitivity must be a highly significant factor in any consideration of the mechanism of narcotic action.

The total respiration of tissues other than brain is also affected by narcotics, though not to the same degree. A result with evipan is shown in

¹³ Quastel, Tennenbaum and Wheatley, *Biochem. J.*, 1936, 30, 1668; Mann, Tennenbaum and Quastel, *ibid.*, 1938, 32, 243.

Table V.¹³ Examination¹³ of the inhibitory action of narcotics on the respiration of a variety of tissues has shown that narcotics inhibit the oxidation of glucose, lactate and pyruvate in tissues such as liver, kidney or diaphragm to about the same extent as in brain. It is difficult, however, to state in quantitative terms the inhibitory action of, say, luminal on substrate oxidations by liver or kidney owing to the relatively rapid change of inhibition with time and the effect of the drug on the respiration of the tissue in absence of added substrate. It would seem, on the whole, that the effects of low concentrations of narcotics are confined as with brain to the inhibition of substances important in carbohydrate metabolism. With brain, however, in contrast to such tissues as liver and kidney, carbohydrate breakdown seems to be the dominant feature of metabolism and it is this fact which throws into prominence the specific inhibitory effects of narcotics in brain metabolism.

Reversibility of Narcotic Action *in vitro*.

The effects of narcotics such as the barbiturates or chloretone, or hyoscine, on the respiration of brain cortex slices are not irreversible. This is shown¹⁴ simply by washing the brain slices in a narcotic-free medium after their immersion for an hour at 37° in the narcotic solution. The low and steady oxygen uptake found in presence of the narcotic is raised immediately to a higher level which also remains steady. A typical result, with chloretone as the narcotic, is shown in Table VI.¹⁴ Results showing the attainment of steady rates of respiration by brain cortex slices in presence of low concentrations of urethane, avertin or luminal are shown in Figs. 1, 2 and 3.¹⁴ High concentrations of narcotics, however, produce irreversible effects.

TABLE VI.—GUINEAPIG BRAIN CORTEX SLICES IN PHOSPHATE-Locke-Glucose MEDIUM.

	Q_{O_2} (Respiration).
1a. In absence of narcotic	15.5
1b. After washing and reimmersion in fresh medium	14.2
2a. In presence of 0.002 M. chloretone	5.8
2b. After washing and reimmersion in fresh narcotic free medium	12.0

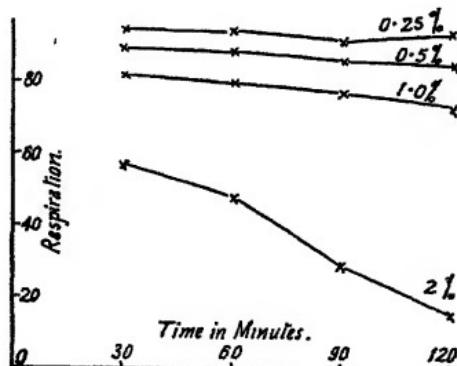


FIG. 1.—Effect of ethylurethane on the respiration of rat brain cortex in presence of glucose (Jowett).

equation (Jowett,¹⁴), as observable with small concentrations of narcotic

Analysis of the data indicates that two effects of a narcotic on respiration of brain *in vitro* take place:

- (1) Rapid attainment of an equilibrium between the narcotic and a constituent of the respiratory system. The inhibition of respiration is that to be expected from a simple mass action

¹⁴ Quastel and Wheatley, *Biochem. J.*, 1934, 28, 1521.

producing inhibitions not greater than 40 %. This applies to narcotics such as urethane, chloral, chloretone, barbiturates, avertin (tribromethyl alcohol) and magnesium ions.

(2) Relatively slow development of irreversible changes, leading to increased inhibitions of respirations which cannot be restored to normal by removal of narcotic. This takes place with most narcotics but is only observable at relatively high concentrations with narcotics such as barbiturates or chloretone. It occurs, however, at low concentrations with ether¹⁷ and ethyl alcohol.¹⁴ Irreversibility

of action also occurs with indole¹⁸ which is also a powerful inhibitor of brain respiration. The reasons for these irreversible changes are obscure.

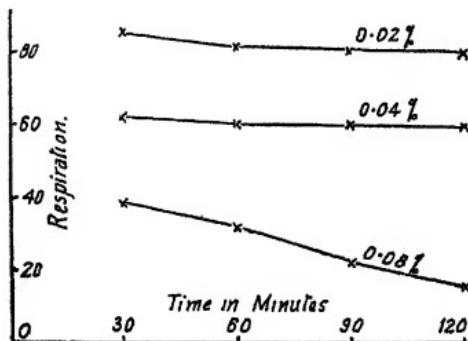


FIG. 2.—Effect of avertin on the respiration of rat brain cortex in presence of glucose (Jowett).

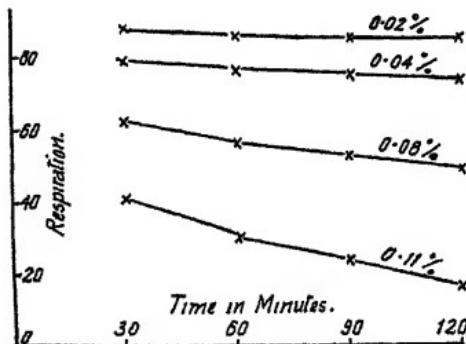


FIG. 3.—Effect of luminal on the respiration of rat brain cortex in presence of glucose (Jowett).

concentrations is very much greater than with the higher K⁺ concentration (see Fig. 4¹⁹). The concentration of K⁺ normally present in serum is sufficient to stabilise the inhibition due to the narcotic. When the temperature of the experiment usually carried out at 39° is dropped to 29° the inhibitory effect of a narcotic such as chloretone no longer varies appreciably with the K⁺ (see Fig. 5¹⁹). A steady inhibition is found whether the K⁺ is high or low. The increasing inhibition at 39° due to low concentrations of K⁺ is possibly due to loss of K⁺ from the nerve cell at the low external concentration or to loss of some other cell constituent

Effects of Potassium Ions.

Another phenomenon bearing upon the inhibitory effects of small concentrations of narcotics may now be considered. The steady state of the diminished respiration of brain slices brought about by small concentrations of narcotics such as luminal or chloretone is found to be greatly dependent on the concentration of K⁺ in the medium. With such high concentrations of K⁺ as 0.0128 M.—double that normally present in serum—a steady inhibition is quickly attained by chloretone. At low concentrations of K⁺, e.g. 0.002 M., however, the respiration is found to drop quickly in presence of narcotics to the level found with the higher K⁺ concentrations, to remain at this steady state for a short period and then to fall quickly so that eventually the inhibition found with low K⁺ con-

concerned with cell respiration, due to irreversible changes in the cell which proceed more slowly when the temperature is lowered.

Narcotics and Substrate Concentration.

If a narcotic enters into a mass action equilibrium with an enzyme with which the substrate oxidised by the brain is also combined, it would be expected that increase in substrate concentration would lead to a diminution in the inhibitory power of the narcotic. Results given in Table VII¹⁸ show that this does not take place. An eight-fold increase in concentration of sodium pyruvate has no effect on the inhibition of oxygen uptake of rat brain cortex due to chloretone.

This shows that the narcotic must enter into equilibrium with some component of the respiratory system which is independent of the substrate burned.

Yet this conclusion is opposed to that obtained from the study of narcotic inhibition of brain dehydrogenations carried out under anaerobic conditions.¹⁸

Narcotics and Dehydrogenases.

In a study¹⁸ of the inhibitory effect of chloretone on lactic dehydrogenase of minced brain tissue, it was found that the narcotic and substrate (sodium lactate) competed, according to the mass action law, for the enzyme. The enzyme was studied in the usual way by determining the rates of reduction under anaerobic conditions of a dyestuff, methylene blue, in presence of the tissue and mixtures of varying concentrations of narcotic and substrate.

It had long been known that narcotics inhibit dehydrogenases and it seemed a simple explanation of narcotic inhibition of brain respiration to suppose that the effect was due to inhibition of dehydrogenases affecting either glucose, or lactate or pyruvate. The results given in Table VII show that this cannot be the case. Yet the effect of the narcotic is not connected with the enzymes concerned with the activation of oxygen itself, as inhibitive concentrations of narcotics do not affect the oxidation of sodium succinate or *p*-phenylene diamine.

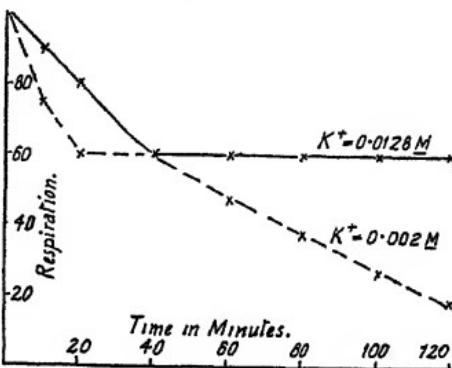


FIG. 4.—Effect of 0.033 % chloretone on the respiration of rat brain cortex in presence of glucose at 39° C. (Jowett and Quastel).

Temp. = 39° C.

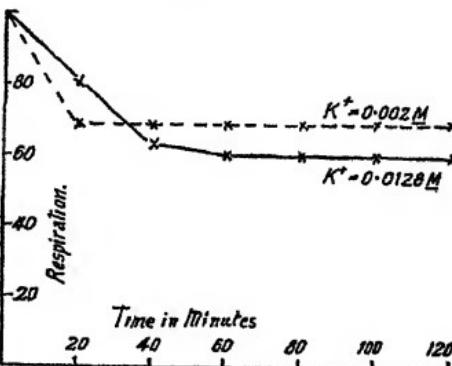


FIG. 5.—Effect of 0.033 % chloretone on the respiration of rat brain cortex in presence of glucose at 29° C. (Jowett and Quastel).

Temp. = 29° C.

TABLE VII.—EFFECT OF SUBSTRATE CONCENTRATION ON INHIBITIONS OF BRAIN CORTEX RESPIRATION (Q_{O_2}) BY NARCOTICS.

Animal.	Substrate.	Narcotic.	% Inhibition of Q_{O_2} .
rat . .	Na Pyruvate 0.01 M	Chloretone 0.037 %	37
	" 0.08 M.	"	37
uninecapig .	" 0.06 M.	Luminol 0.08 %	27
	" 0.01 M.	"	28
" . .	Na d. Lactate 0.06 M.	"	39
	" 0.01 M.	"	31

A clue to the solution of this anomaly may be found in the fact that the low concentrations of narcotics which are highly inhibitory aerobically have but little inhibitory effect anaerobically. Thus chloretone is ten times less effective in securing an inhibition of lactic acid oxidation in presence of brain anaerobically than under aerobic conditions.

A possible explanation is that the narcotic, at the low concentrations effective under aerobic conditions, exerts its main effect on a part of the respiratory system which is inert or functionless under anaerobic conditions. That such a part of the respiratory system has the properties of an enzyme structure is evident from the fact that it is affected by surface active narcotics of so many different chemical types. It must, however, be a tissue component with a much higher affinity for narcotics than the most sensitive enzymes—the dehydrogenases—with which we are so far familiar.

If this view is true the inhibitions of respiration of intact brain tissue obtained by low concentrations of narcotics under aerobic conditions are not due to competition of the narcotics with the substrates (e.g., lactic or pyruvic acid) for their dehydrogenases but to the affinity of the narcotics to a special component playing a highly important part in the chain of reactions composing the complete aerobic respiratory process of the cell.

Narcotics and Glycolysis.

Confirmation of the fact that narcotics at low concentrations do not affect the known dehydrogenases comes from the entire absence of any inhibition by a narcotic such as chloretone on anaerobic glycolysis by brain cortex (see Table VIII¹⁸).

TABLE VIII.—EFFECT OF CHLORETONE ON ANAEROBIC GLYCOLYSIS (Q_{M^2}) OF RAT BRAIN CORTEX.

Conc. of Narcotic.	O_{M^2}
Nil . .	15.2 19.8
0.033 %	15.1
0.05 %	16.4

The mechanism of anaerobic breakdown of glucose in brain is not yet clear but if the reactions involved are similar to those taking part in the anaerobic breakdown of glucose in muscle or yeast, an interplay of dehydrogenase systems will be involved. The results show that if a narcotic-sensitive dehydrogenase system plays an important role in the aerobic breakdown of glucose it

is either absent from, or is without influence in, the reactions involved in the anaerobic breakdown of glucose by brain.

Narcotics and an Intermediate Respiratory Component.

An investigation¹⁹ of respiratory systems made up from isolated tissue components, e.g., muscle dehydrogenases, and preparations of cozymase,

¹⁸ Michaelis and Quastel, *Biochem. J.*, 1941, 35, 518.

flavoprotein, and cytochrome, oxidase, and studied under both aerobic and anaerobic conditions, has shown that the effect of narcotics at low concentrations is restricted to a tissue component, which is possibly a flavoprotein. This is illustrated in Fig. 6 which shows the narcotic sensitive and insensitive regions of a narcotic sensitive respiratory system.¹⁹ It is impossible, however, with our present incomplete knowledge of the components of respiratory systems, to state definitely which component is specifically affected at the low concentrations of narcotics which inhibit brain respiration. It is, however, a step forward to realise that a special component of the respiratory system is highly narcotic sensitive, and that the effects of narcotics at biologically important con-

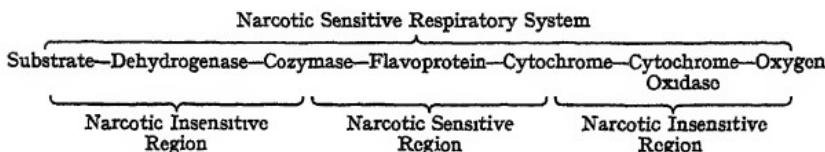


FIG. 6.

centrations are not to be attributed, as has been supposed in the past, to a general inhibition of dehydrogenases by non-specific surface adsorption of the narcotics.

Benzedrine and Amine Oxidase of Brain.

It is well known that benzedrine administration has a considerable value in cases of narcolepsy and in conditions where a stimulation of the central nervous system is required.

The addition of benzedrine at low concentrations to brain cortex respiring in a glucose medium neither increases nor decreases the respiration, nor will it neutralise the diminution of respiration due to the presence of a narcotic.

It is possible, however, that the relation of benzedrine to amine oxidation in brain may be connected with its clinical effects.

It has been known for some time²⁰ that the presence of amines such as tyramine or isoamylamine brings about a marked diminution (increasing with time) in the respiration of brain examined *in vitro*. The addition of benzedrine, however, to brain cortex respiring in the presence of tyramine and other inhibitive amines has been found to neutralise, or partly neutralise, the inhibition.²¹ A typical result is shown in Table IX.²¹

TABLE IX.—EFFECTS OF BENZEDRINE ON RAT BRAIN CORTEX RESPIRATION IN PRESENCE OF TYRAMINE IN A GLUCOSE MEDIUM.

Tyramine M. Conc.	Benzedrine M. Conc.	Q _{O₂}		
		1st Hour.	2nd Hour.	3rd Hour.
0 . .	0	11.4	10.1	9.0
1.9 × 10 ⁻³ .	0	9.6	5.3	3.1
1.9 × 10 ⁻³ .	1.4 × 10 ⁻⁴	10.1	8.5	6.3

²⁰ Quastel and Wheatley, *Biochem. J.*, 1933, 27, 1609.

²¹ Mann and Quastel, *ibid.*, 1940, 34, 414.

The fall in brain respiration due to the presence of tyramine, etc., is not due wholly to the amine itself but to a product of oxidation of the amine, i.e., the corresponding aldehyde. Benzedrine owes its stimulating action in brain respiration in presence of inhibitive amines to its ability to compete reversibly with amines for the amine oxidase of brain, thereby reducing the rate of formation of the inhibitory aldehyde.

Competition for amine oxidase takes place between various amines. Pugh and Quastel²² found that competition takes place between the following amines: tyramine, isoamylamine, β -indoethylamine and β -phenylethylamine. Blaschko *et al.*²³ showed that competition occurs between tyramine, adrenaline, isoamylamine and β -indoethylamine.

They also showed that *l*-ephedrine, triethylamine, triisoamylamine, hordenine—amines which are either slowly or not attacked by amine oxidase—have an affinity for the enzymes and inhibit the oxidation of amines which are attacked by the oxidase. Benzedrine is either very feebly or not at all attacked by amine oxidase. It has nevertheless a high affinity for this enzyme and is a powerful inhibitor of amine oxidation.

It has been proved that amines combine with amine oxidase according to the mass action law and that competition between the amines takes place in strictly reversible manner. Taking the dissociation constant of the tyramine-amine oxidase complex to be 0.00178,²² the dissociation constants for benzedrine—and other amine-amine oxidase complexes have been worked out.

These are shown in Table X.²¹

The effects of benzedrine *in vitro*, in partially neutralising the inhibition of glucose oxidation by brain due to the presence of tyramine and other amines, take place at concentrations which are not markedly greater than those which have pharmacological effects *in vivo*. Moreover, since competition between benzedrine and other amines takes place at amine oxidase according to the laws of mass action, it follows that the influence of benzedrine may be exerted in the body at much lower concentrations than have been used in *in vitro* investigations. It seems not unreasonable to suggest that the action of benzedrine *in vivo* is linked with its ability to compete with amines which give rise by oxidation to toxic substances; the lower the concentrations of such amines the lower the quantity of benzedrine which will be required to compete successfully with them.

²² Pugh and Quastel, *Biochem. J.*, 1937, 31, 2306.

²³ Blaschko, Richter and Schlossman, *ibid.*, 1937, 31, 2187.

TABLE X.

Amine.	Dissociation Constant of Amine Oxidase Complex with Amine.
 Tyramine . . .	0.00178
 Benzedrine . . .	0.0004
 Adrenaline . . .	0.0004
 l-Ephedrine . . .	0.0057

Ephedrine is known clinically to be less powerful than benzedrine as a stimulant of the central nervous system and it has been shown that such a difference between their effects on brain respiration occurs also *in vitro*. According to Gunn *et al.*²⁴ 3:4 methylene dioxyphenylisopropylamine is a somewhat more powerful stimulant of the central nervous system than benzedrine and it has at least the same activity as benzedrine in neutralising the fall of brain respiration in a glucose medium due to tyramine. Again, according to Gunn *et al.*²⁴ 3-methoxy-4-hydroxyphenyl-isopropylamine is a less powerful stimulant of the nervous system than benzedrine. The result is consistent with the relatively poor activity of the former amine in neutralising the inhibitory action of tyramine on brain oxidation.²¹ Such results are suggestive of a possible connection between amine metabolism in the brain and the development of the clinical condition known to be relieved by benzedrine administration.

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²⁴ Gunn, Gurd and Sachs, *J. Physiol.*, 1939, 95, 485.

GENERAL DISCUSSION

Dr. H. McIlwain (Sheffield) (communicated) : Studies of the action of narcotics on bacteria²⁵ have given results which may be relevant to their action in the systems examined by Dr. Quastel and referred to also by Dr. Hurst and Dr. Ing. It was concluded that narcotics (ether, alcohol, chloroform, ethylcarbonate, novocaine) acted by reversibly denaturing enzymes of dehydrogenase systems, the critical evidence being antagonism of their action, by increased hydrostatic pressure. The antagonism was explained through the increase in volume accompanying denaturation, and was not found with bacterial inhibitors known to act differently, e.g. with sulphanilamide. The absence, found in several cases by Dr. Quastel, of antagonism to narcotics by substrate molecules is then understandable, but differences in susceptibility of proteins to reversible denaturation, and their varying importance to the cell, permits the specificity of action emphasised by him.

²⁵ Johnson, Brown and Marsland, *Science*, 1942, 95, 200; *J. Cell. comp. Physiol.*, 1942, 20, 269; Johnson, Eyring and Williams, *ibid.*, 1942, 20, 247.

RELATIONS BETWEEN *IN VIVO* AND *IN VITRO* ACTIONS OF CHEMOTHERAPEUTIC AGENTS.

By HENRY McILWAIN.

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Study of the relation between the action of chemotherapeutic agents on the course of microbial infections, and upon the parasites alone, is a means of analysing the complex system presented in practice by the host, parasite, and drug. As activity or inactivity of the agents is conditioned much more by the nature of the parasite than by that of the host, they have been expected to exhibit some action on the parasite outside the host. Such action has not always been found and, in consequence, various types of interactions between drug and host have been postulated. Most of

these are discredited, but of them, the conversion of the drug to more active forms undoubtedly occurs *in vivo* in certain cases. Most important among other causes of apparent *in vitro* inactivity of therapeutically active agents are inadequacies in the technique of *in vitro* experiments. Notable instances are afforded by the poor cultural conditions under which pathogenic trypanosomes and amoebae were first studied, which prevented observation of the effect of agents whose action was not manifest in a few hours; for the parasites soon died.^{1, 2} The present account emphasises other instances which show that, for chemotherapeutic studies, culture media must not merely be adequate for growth, but must simulate conditions in the host in respect to their concentrations of specific substances, commonly occurring in animals and media, which antagonise drug action.

Actions of the Host on the Drug; Types of *in vitro* Activity.

Before considering those interactions which are susceptible to *in vitro* study, it is necessary to emphasise some basic ones which are not. For the purpose of quantitatively comparing the action of a compound *in vitro* and *in vivo*, it is at present necessary to administer it to animals and find what concentrations can be attained in relevant sites without damage to the animal. The levels are demonstrably conditioned by a combination of absorption, metabolism, and excretion. Some of these processes can be studied *in vitro*—e.g., the acetylation and inactivation of sulphanilamide by the liver, or the conversion of Prontosil to the active sulphanilamide by various tissues.³

The type of *in vitro* action which is associated with activity of an agent *in vivo* has often been assumed to be the killing of the parasite. This, however, occurs only in some cases. Acriflavine was found to be primarily bacteriostatic *in vitro*, and it was emphasised that such an action, combined with the normal behaviour of the host towards non-invasive bacteria, was adequate for disinfection *in vivo*.⁴ This has been reiterated with respect to the sulphonamides. From the many observed and postulated activities of the sulphonamides, which have included the stimulation of defences of the host and various actions on the parasites, their bacteriostatic action has been accepted as adequate to explain *in vivo* activity.^{5, 6} Although it is not necessarily a general conclusion that inhibition of growth is the basis of bacterial chemotherapy, no case which has been fully investigated is inconsistent with the suggestion. It has been successfully used as a working hypothesis; other actions are examined below.

Natural Occurrence of Compounds Antagonistic to Chemotherapy.

An early instance of a specific participation of the host in chemotherapy was encountered in the activation of certain arsenicals by their conversion to arsine oxides. Conversion to a more active compound was also observed with Prontosil, and when some workers found sulphanilamide itself to be inactive *in vitro*, this also was referred to interactions between the drug and the host. In this case, however, reports of *in vitro* studies were not consistent, some observers finding the compound highly active. Many of these discrepancies were explained in a series of papers, now very familiar, in which they were shown to be largely due to different media; material was extracted from various organic sources which prevented the

¹ Yorke and Murgatroyd, *Ann. Trop. Med. Parasitol.*, 1930, 24, 449.

² Dobell and Laidlaw, *Parasitology*, 1926, 18, 266.

³ Marshall, Jr., *Physiol. Rev.*, 1939, 19, 240; *Ann. Rev. Physiol.*, 1941, 3, 643.

⁴ Browning and Gulbransen, *J. Hyg.*, 1919-20, 18, 33.

⁵ Fleming, *Proc. Roy. Soc. Med.*, 1940, 33, 487.

⁶ McIlwain and Hawking, *Lancet*, 1943, I, 449.

bacteriostatic action of the drug, and the main antagonist was shown to have the properties of *p*-aminobenzoic acid. Thus the greater *in vivo* activity of sulphanilamide was referred to a phenomenon which was more familiar in chemotherapy as having the opposite effect. The more usual action is illustrated by the *in vivo* inactivity of mercuric compounds, which was shown due to their combining with a particular protein of serum,⁷ or by some phenolic compounds, which were sufficiently active in broth to give expectations of *in vivo* activity, but again were antagonised by serum though no evident combination occurred.⁸ On the other hand, the activity of acriflavine was greater in serum than in broth, though it was lowered by pus; here again, specific materials have been implicated.⁹ Clearly, therefore, there are different types of antagonistic compounds, of varying natural occurrence, which interfere in different ways with the actions of various chemotherapeutic agents and whose activities must be assessed before the activity of a given concentration of an agent *in vitro* can be compared with that *in vivo*.

Nature of Drug Antagonists.

The nutritional relationship between host and parasite is a fundamental one, and was early emphasised in relation to chemotherapy. Analogies were indicated between the action of drugs and conditions of poor nutrition,¹⁰ and related to such a conception is the regarding of drug-antagonists as nutrients or as stimulating the proliferation of the parasite.¹¹ With growth of biochemical knowledge, the importance to living organisms of compounds other than those assimilated as foodstuffs has been made evident, and Voegtlin¹² found one such metabolite to be a drug-antagonist: phenylarsine oxides formed dissociable compounds with glutathione and other thiol compounds which annulled their trypanocidal action *in vivo* and *in vitro*. Moreover, he suggested such combination as a basis not only for antagonism of the arsenicals, but also of their action upon the parasite, for thiol compounds were known to be of critical importance in living processes. The actions of many inhibitors on metabolic processes had been investigated at the time when sulphanilamide-antagonism was being studied, and Woods¹³ applied the knowledge that enzymes can be inhibited by compounds structurally related to their substrates, in suggesting *p*-aminobenzoic acid as both an essential metabolite¹⁴ to the bacteria, and as the compound responsible for antisulphanilamide activity in his preparations.

The relationship between sulphanilamide and *p*-aminobenzoate proved an extremely specific one, though other compounds, notably purines and methionine, antagonised the action of sulphanilamide in other ways.¹⁵ Consequently the demonstration that the interactions occurred *in vivo*¹⁶ as well as *in vitro* was valuable evidence that the anti-streptococcal action of sulphanilamide *in vivo* was indeed the same as that *in vitro*. The *in vivo* antagonism of pentavalent arsenicals by thiol derivatives had previously been used as evidence of the similarity of their action to that of the arsine oxides and thus to confirm the suggestion that the pentavalent compounds functioned only after their reduction in the host.¹⁷

Results suggestive of the natural function of drug-antagonists have

⁷ Smith, Czarnetzky and Mudd, *Amer. J. Med. Sci.*, 1936, 192, 790.

⁸ Bechhold and Ehrlich, *Hoppe-Seyl. Z.*, 1906, 47, 173.

⁹ McIlwain, *Biochem. J.*, 1941, 35, 1311.

¹⁰ Braun and Schaeffer, *Z. Hyg. Infect. Kr.*, 1919, 89, 339; Stearn, E. A. and Stearn, E. W., *J. Bact.*, 1924, 9, 491.

¹¹ Lockwood, *J. Immunol.*, 1938, 35, 155; Green, *Brit. J. exp. Path.*, 1940, 21, 74.

¹² Voegtlin, *Physiol. Rev.*, 1925, 5, 63.

¹³ Woods, *Brit. J. exp. Path.*, 1940, 21, 74.

¹⁴ Fildes, *ibid.*, 1940, 21, 67.

¹⁵ Kohn and Harris, *J. Pharmacol.*, 1943, 77, 1.

¹⁶ Selbie, *Brit. J. exp. Path.*, 1940, 21, 90; Martin and Fisher, *J. biol. Chem.*, 1942, 144, 287.

also been obtained by designing inhibitors to interfere with known bacterial metabolites,¹⁷ assuming them to be related to enzyme systems which could be regarded as potential drug-receptors.¹⁸ Many compounds, structurally related to such metabolites were found inhibitory, and their actions in most cases were antagonised by the metabolites used as models. Consideration of the naturally-occurring concentrations of their antagonists showed that some would not be expected to be active *in vivo*. Pantoytaurine,¹⁹ however, inhibited streptococci *in vitro* in the presence of the concentration of pantothenate (its main antagonist) in rat blood, to degrees comparable with those associated with therapeutic activity in sulphanilamide,²⁰ when present in concentrations which could be attained in rats. Action *in vivo* was hence anticipated,²¹ and found; here also the essential similarity of the action *in vivo* and *in vitro* was shown by preventing the *in vivo* action with more pantothenate.

Varying Occurrence and Metabolism of Drug Antagonists.

The concentration of an inhibitor necessary for bacteriostasis *in vitro* is in some cases roughly proportional to the coincident concentration of antagonists;^{15, 17, 20} other relationships have been found in other cases,^{9, 17} but all emphasise that the naturally occurring concentrations of drug antagonists, and their alteration by metabolism of the host, can be as important to the action of a drug *in vivo* as can the concentration and metabolism of the drug itself. Thus, sulphonamide antagonists presented some puzzling phenomena. The quantities of *p*-aminobenzoate needed for preventing the antistreptococcal activity of sulphanilamide when the two compounds were fed or injected together,¹⁸ were about 500 times those which were effective *in vitro*.¹⁹ Again, the quantities of sulphanilamide needed for antistreptococcal action in untreated tissue fluids or simple extracts were only a fraction of those needed in the presence of other extracts (e.g., some bacteriological broths) or autolysates (e.g., pus). These results were explicable by the action of the host on one of the drug antagonists, either in conjugating *p*-aminobenzoate when administered or in liberating it from combined forms on autolysis.¹⁹ Normal human blood and urine, indeed, were found to contain quantities of combined *p*-aminobenzoate in great excess of that needed to antagonise the anti-streptococcal action of the highest sulphonamide levels attainable *in vivo*. This indicates the vital importance of some normal mechanism, possibly acetylation, to all sulphonamide therapy. Of practical importance is the finding that sulphonamide activity *in vivo* is antagonised by certain local anaesthetics.²² Those contained *p*-aminobenzoate and their activity had first been demonstrated *in vitro*;¹⁸ the *in vivo* activity was not great, presumably for the reasons discussed in relation to *p*-aminobenzoate itself.

Allied to those results is the finding that azochloramid potentiates the sulphonamides;²³ the action extends to *in vivo* conditions and has been explained as a destruction of sulphonamide antagonists,²⁴ including those synthesised by the parasite itself. The finding should be of more general application, and microbial destruction and synthesis of drug antagonists is known, which can afford a basis for both greater and lesser susceptibilities of mixed infections, to a given drug.

Considering again conditions in the host, notable differences are known

¹⁷ McIlwain, *Brit. J. exp. Path.*, 1940, 21, 136; *ibid.*, 1941, 22, 148; Fildes, *ibid.*, 1941, 22, 293.

¹⁸ McIlwain, *Lancet*, 1942, I, 412.

¹⁹ McIlwain, *Brit. J. exp. Path.*, 1942, 23, 265.

²⁰ McIlwain, *ibid.*, 1942, 23, 95.

²¹ de Waal, Kanaar and McNaughtan, *Lancet*, 1942, 2, 724.

²² Neter, *J. Pharmacol.*, 1942, 74, 52; *J. Bact.*, 1942, 44, 261.

²³ Schmelkes and Wyss, *Proc. Soc. exp. Biol., N.Y.*, 1942, 49, 263.

to exist in the concentrations of metabolites, including drug antagonists, in different animal species.²⁴ The values for pantothenate (antagonising pantoyltaurine) in the same tissues of different animals (mouse, rat, hog and cow) could vary over a three-fold range, and during the life of a given species showed variations up to four-fold, with maxima in different tissues and different animals occurring at different times. Concentrations of nicotinic acid derivatives (relevant to the action of certain sulphonamides)²⁵ were found to be more constant, but of riboflavin (partly antagonising acriflavine²⁶) in different species showed a variation greater than ten-fold, the maximum again being different in time in different species and organs. A point of special importance in relation to animal testing of chemotherapeutic agents is the finding of a general tendency to inverse relationship between the size of animal and the level of essential metabolites, including drug-antagonists, in their tissues.²⁴ This would tend to cause lesser action or inactivity in, e.g., mice, with agents which might be active in the larger animals with which chemotherapy is ultimately most concerned. Such results have been obtained,^{2, 6, 26} and sometimes referred to varying metabolism of the drug; the present considerations offer alternative explanations. The general rough agreement in chemotherapeutic effects in hosts of different species is paralleled by the finding that differences in metabolite levels in different species was not commonly greater than ten-fold. Complete differences in metabolism of compounds related to drug antagonists are, however, known to exist in different animal species, e.g., the unusual reaction of fowls to substituted benzoic acids, or of man to phenylacetic acids.²⁷

Actions of Chemotherapeutics on Parasites *in vitro*, other than those on Growth.

Many attempts have been made to correlate the actions of chemotherapeutic agents with properties other than their effects on growth; those relating to purely chemical and physical properties will be discussed by other contributors.

Metabolic methods have been used to measure growth of organisms, and so indirectly to show parastostatic or parasiticidal action,^{28, 29} but this section is intended to consider the more direct action of inhibitors on metabolic processes. Sulphanilamide appears to have no action on respiration³ at concentrations at which it inhibits growth and is active therapeutically, though non-specific effects occur with higher concentrations. Sulphapyridine affects the oxidation of three-carbon compounds, though this action, unlike the major effects of the drug, is not antagonised by *p*-aminobenzoic acid.²⁵ Many simple antibacterial agents (mercuric salts, phenols, iodine) inhibit respiration of *Bact. coli*, as also does rivanol, and such inhibition has been suggested as a measure of germicidal powers; its connection with bacteriostasis is not, however, very close, and the instance of sulphanilamide would preclude its general application to chemotherapy. Metabolic methods have also been used in assessing the action of antimalarials on the protozoa;³⁰ in this case the experiments were performed

²⁴ Williams and others, *Studies on the Vitamin Content of Tissues*, I and II; Univ. Texas Publ. 4137 and 4237, 1941 and 1942. The values quoted were found by microbiological assay after standardised processes of extraction.

²⁵ Dorfmann and Koser, *J. inf. Dis.*, 1942, 71, 242.

²⁶ Schlossberger, *Z. Hyg. InfectKr.*, 1928, 108, 627.

²⁷ Harrow and Sherwin, *Textbook of Biochemistry*, Saunders, 1935.

²⁸ Greig and Hoogerheide, *J. Bact.*, 1941, 41, 557; Hirsch, *Studien über die mikrobiologischen Grundlagen der Sulphanilamid-Therapie*, 1942, Kenan Basimevi, Istanbul.

²⁹ Bronfembrenner, Hershey, and Doubley, *J. Bact.*, 1939, 37, 583.

³⁰ Fulton and Christophers, *Ann. Trop. Med. Parasitol.*, 1938, 32, 77; Wendel, *J. biol. Chem.*, 1943, 148, 21.

in body fluids with little modification, but much of the work with bacteria has used media whose content of drug antagonists may be very different from that *in vivo*. Many examples of the action of chemotherapeutic agents on particular enzymes can be given,³¹ and in some cases parallelism has been reported between actions on enzymes, and therapeutic activity; such a relation was found between trypanocidal and anti-lumarase action, though it is not necessarily considered of functional importance.³² Indeed, the actions which have been most fully investigated, as those of the sulphonamides on carbonic anhydrase or peroxidase, have been shown to be unrelated to the action on the parasite. Evidence is not available concerning others, such as the high activities of quinine or atoxyl on lipases. Lack of correlation of antibacterial action with both overall respiration, and with effects on such enzyme systems as have been studied, emphasises the biochemical specificity of chemotherapeutic agents. The present ignorance of their detailed mode of action is paralleled by ignorance of that of many other compounds which exert critical effects on living organisms.

In vitro Investigations of Actions of Drugs on Tissues and Processes of the Host.

It follows from the knowledge that some chemotherapeutic agents are primarily bacteriostatic, that natural defences of the host are of critical importance in their use; but not all these processes are susceptible to *in vitro* study. Special attention has been given to the action of acriflavine⁴ and other acridine derivatives³³ on phagocytosis, and the motility of leucocytes. Many observers, in studying the effects of sulphonamides on phagocytosis, had been expecting the drugs to increase such activity, but an assessing of various reports³ suggests that the compounds have little if any action upon the process other than that referable to the action of the drugs on the bacteria. This is emphasised by observations with sulphapyridine in infections of mice in which the reactions of the host differed with different parasites: the response to streptococci and drug being phagocytosis, but to pneumococci with the same drug, the development of immune bodies.³ Antibodies have been observed *in vitro* to convert a bacteriostatic effect of sulphanilamide to a bactericidal one.¹ Again, in treatment of trypanosomiasis, immunity follows chemotherapy but its grade depends upon the strain of parasite and not upon the chemotherapeutic agent.³⁴ In view of these widely different cases of varying reactions of the host to inactivation of organisms by the same drug, special evidence would be needed to support hypotheses of a drug exerting a major direct effect upon the host's defences.

In vitro studies of the effects of chemotherapeutics upon tissues of the host have also been made by tissue-culture and manometric methods. The value of *in vitro* observation of simultaneously growing tissues and parasites was emphasised in 1916,³⁵ but many reports have concerned only the brief exposing of tissues and bacteria to the agent, not necessarily in body fluids or solutions equivalent in content of antagonistic compounds.^{36, 37} The sulphonamides were found to have extremely little action on chick embryo tissues in a critical study in which other differences between conditions in culture and in the animals are discussed: the

³¹ Clark, Heffier's *Handbuch der Experimentellen Pharmakologie*, 1937, suppl. vol. 4.

³² Quastel, *Biochem. J.*, 1931, 25, 1121.

³³ Albert, Francis, Garrod, and Linnell, *Brit. J. exp. Path.*, 1938, 19, 41.

³⁴ Browning, *System of Bacteriology*, Med. Res. Council, Lond., 1931, 6, 301.

³⁵ Lambert, *J. exp. Med.*, 1916, 24, 683.

³⁶ Salle, McOmie, Shechmeister, and Foord, *J. Bact.*, 1939, 37, 639.

absence of circulatory and detoxicating mechanisms, and varying resistances of tissues from different animals.³⁷

Manometric methods have also tended to ignore the importance of natural antagonists and of bacteriostatic effects in comparing the actions of compounds upon tissue and parasite. Decrease in respiration or glycolysis is commonly measured, and the relation of such a property to the actions of the agents in chemotherapy can only be established empirically, and can vary with the agent and tissue, which limits the value of the methods for even comparative purposes. Nevertheless, their potential value in selecting compounds suitable for use as antiseptics in brain operations has been shown.³⁸ In this case the problem itself defined the tissue to be used, but for more general purposes the choice appears to be arbitrary. Variations in concentration of drug antagonists are extremely large in different tissues, those of human origin varying twenty- to twenty-five-fold in their riboflavin and pantothenate contents, and six-fold in that of nicotinic acid derivatives.³⁹

Special Effects of Chemotherapeutics on Parasites, Exhibited *in vivo* and *in vitro*.

In addition to the specific interaction between chemotherapeutic agents and their natural antagonists, referred to above, two related¹⁸ types of behaviour, first observed *in vivo*, have been reproduced *in vitro*. These are drug resistance and chemotherapeutic interference.

Evidence was given for drug-resistance in trypanosomiasis, in which it was first observed, being conditioned largely by the host; but such a conclusion has been discredited.⁴⁰ Trypanosomes made resistant in one host have been found resistant in others, and *in vitro*; resistant organisms prepared *in vitro* can be resistant *in vivo*. Here the success or failure of chemotherapy is conditioned by an experimentally induced change in the parasite alone. Evidence has not been encountered for a drug alone causing a comparable change in a host, which persisted after the drug had been excreted; though a drug in the presence of the parasite *in vivo* can result in a lasting change in the natural defences of the host. Reasons other than drug-resistance in the parasite can, of course, condition failures in treatment, but after taking such factors into account a considerable number of such failures have been directly referred to properties of the parasite which can be demonstrated *in vitro*.^{39, 40} Results with sulphonamides present closely analogous features and make the conclusions reached with respect to non-bacterial infections more general. Strains produced by use of one sulphonamide, *in vivo* or *in vitro*, are commonly resistant to all drugs of the group, though some specificity has recently been found in respect to *Shigella* strains.⁴¹ Accurate measurement of the resistance of *Bac. coli* strains to different sulphonamides has also shown their relative resistance to sulphanilamide and sulphathiazole to vary with the media in which they were tested.⁴² This is readily understandable in terms of drug antagonists and could conceivably give a basis for small differences in resistance of a given organism in different hosts on account of their varying blood constituents.

Chemotherapeutic interference was first observed between acriflavine and parafuchsin, with trypanosomes in mice.⁴³ It has since been

³⁷ Jacoby, Medawar, and Willmer, *Brit. Med. J.*, 1941, 2, 140.

³⁸ Manifold, *Brit. J. exp. Path.*, 1941, 22, III.

³⁹ Yorke and Hawking, *Ann. Trop. Med. Parasitol.*, 1932, 26, 215; Yorke and Murgatroyd, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1935, 28, 435.

⁴⁰ Petro, *Lancet*, 1943, 1, 35.

⁴¹ Cooper and Keller, *Proc. Soc. exp. Biol. N.Y.*, 1942, 51, 238.

⁴² Harris and Kohn, *J. Immunol.*, 1943, 46, 189.

⁴³ Browning and Gulbransen, *J. Path. Bact.*, 1922, 25, 395.

observed in other systems, including that of arsenoxides and various dyestuffs with trypanosomes, when parallel effects were found *in vitro*.⁴⁴ Interfering effects on the metabolism of trypanosomes and yeast with acriflavine and parafuchsine have also been reported.⁴⁵ There is thus little doubt that this phenomenon also is independent of the host. The action of acriflavine on *Bact. coli* *in vitro* is reduced by various compounds, including phenosafranine, methylene blue and riboflavin, and interpretations of the phenomena have been given which link it with known effects of inhibitors on metabolic processes. Comparable phenomena are also known to occur in the much simpler system presented by enzymes *in vitro*.⁴⁶

Conclusion.

It is not intended in this survey to disparage the use of animal testing in chemotherapy, but to emphasise (1) that such testing is not necessarily much nearer to the conditions under which the drug will ultimately be used, than are properly chosen *in vitro* conditions; and (2) that suggestions that chemotherapeutics exert a major direct effect upon the host, or that the host in their presence acts upon the parasite in a manner different from that exhibited towards any micro-organism, non-invasive by nature or inhibition, must be carefully re-assessed. *In vitro* testing is known not to reproduce all the conditions of the normal environment of the parasite, but with present knowledge it is less likely to introduce new and unknown factors than is testing in another host. By trial and error, experimental hosts of roughly equivalent behaviour to man with respect to specified drugs may be found, but it would be extremely unlikely for such a relation to apply to a wide range of compounds active against a particular parasite, as such agents can have completely different antagonists whose natural occurrences and metabolism vary independently. The testing of anti-malarials in canaries, though giving results comparable to those of therapeutic practice with some agents, fails with others.⁴⁷ That the agents giving concordant results are those of major importance is to be expected, for the majority were either used in choosing the conditions for the test or devised by it. In order to be discovered by use of the test, new agents must satisfy the stringent condition of activity in two unrelated hosts. Clearly, *in vivo* and *in vitro* examinations of agents are complementary; thus the use of *in vitro* testing in selecting compounds suitable for further examination is valuable, though *in vitro* studies have an analytical importance beyond this. Much still remains to be understood of the manner in which chemotherapeutic agents inhibit parasites, or otherwise render them susceptible to body defences; comparison of *in vivo* and *in vitro* effects has as yet been only semi-quantitative and its further study appears a promising approach to the problem.

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⁴⁴ von Jancso, N. and H., *Z. ImmunForsch.*, 1936, 88, 275.

⁴⁵ Scheff and Hasskó, *Zbl. Bakter.*, I, 1936, 136, 420; Wright and Hirschfelder, *J. Pharmacol.*, 1930, 39, 39.

⁴⁶ Quastel and Yates, *Enzymologia*, 1936, 1, 60.

⁴⁷ Bishop, *Parasitology*, 1942, 34, 1.

GENERAL DISCUSSION

Dr. H. Hurst (Cambridge) (communicated) : The change in drug activity with variation in the carrier medium suggests that carrier activity may play a part by inducing a corresponding change in the functional susceptibility of the test organisms. Since the interpretation of toxicological data *in vivo* must ultimately depend on comparison with *in vitro* tests, a study of the mechanism and limits of carrier activity in physiological media may well fill a gap in our present knowledge of the factors which influence chemotherapeutic activity *in vivo*.

Dr. F. R. Eirich (Cambridge) (communicated) : I should like to draw your attention to one aspect of the problem and to a corresponding experimental possibility which so far has only been touched upon, namely, the action of drugs on protein-structure.

Some years ago McFarlane finally established the existence of pathological serum proteins and investigated their molecular weights in the ultra-centrifuge. Independently we investigated some of the other physico-chemical changes which become apparent in the human serum under pathological conditions. We found very marked and characteristic differences in the course of salt formation and viscosity when the serum was titrated with acids and alkalis, indicating changes in reactivity and molecular volume similar to those which manifest themselves at an early stage of denaturation.

One explanation for this would be to assume structural changes in the ordinary albumins and globulins due to the presence in the blood-stream of parasites or of the products of an abnormal metabolism in the affected part of the host. An alternative possibility would be to connect the changed behaviour with the appearance of new proteins globulin-like in character (antibodies) under the stimulus of pathological conditions (antigens). According to Pauling both phenomena are correlated.

Interesting information as to the action of drugs in this phase could be obtained by comparing, by the viscosity and conductivity method, the influence of chemotherapeutics on the serum *in vivo* and *in vitro*. We began such experiments with promising results, but could not continue owing to war-time conditions, and I wonder why this line of approach has not been incorporated into one of the existing research programmes. There are obviously a number of interesting aspects in such an approach :

(1) One ought to be able to differentiate between drug action in the cell and an eventual one during the preceding circulation.

(2) If there is any immediate action on the serum proteins beyond their carrier function this might, in view of the comparatively less complicated nature of the system, provide valuable clues as to the principles of action.

(3) Again, if the serum proteins are affected following a cellular action of the drug, this might throw some light on Bergmann's hypothesis that the intracellular proteinases play a synthetic role *in vivo*. Proteinases apparently lose their specificity in the presence of peptide mixtures, which, it has been suggested, might be the way foreign proteins change the normal course of protein synthesis. If changes in the serum follow only after drug action in the tissue, this action can be positively identified as taking place in the interior of the cell, and becomes also to some extent specified in its character.

(4) Moreover, rectification of a faulty protein-synthesis or structure might have a direct bearing on the enzymatic activity itself, as its protein component might have been affected.

INTRODUCTORY ADDRESS.

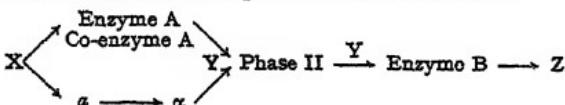
PART II. PHYSICO-CHEMICAL ASPECTS.

BY PROFESSOR E. K. RIDEAL, F.R.S.

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To commemorate the memory of Sir William Hardy the Faraday Society holds from time to time discussions in which an endeavour is made to bring together people who are interested in some particular sphere of biology and those chemists and physicists who are endeavouring to extend our knowledge of the physico-chemical principles involved in the reactions of organised matter.

A number of attempts have been made to explain the mechanism of drug action on simple principles; one may mention the partition principle of Overton, the capillary view of Traube and the specific group concept of Ehrlich as typical. There are many apparent exceptions to such isolated principles. It may be pertinent to the present enquiry to suggest certain implications in the generally accepted concept that between action and response there is likewise implied a passage, or passages, of material from source to sink. We can depict diagrammatically as follows some simple process which involves such a sequence or chain of events.



In the above scheme the reactant X can undergo change to the product Y by alternative paths either through the enzyme system A or the two enzyme systems α and α' . The product Y has then to pass through a separate phase II which may be complex, e.g. a membrane. Y subsequently undergoes change to the product Z by means of the enzyme system B. We may imagine that drug "response" is obtained when the rate of production of product Z is affected. It is clear that this may be brought about in a number of ways. The most direct method is to render the enzyme system B inoperative, by destruction of the protein, by selective adsorption on the prosthetic portion of the enzyme, by reaction with and removal of the co-enzyme or by alteration of the composition, e.g. the pH of the medium B to stop the enzyme activity. A "delayed" response which eventually will be complete will be obtained if both the enzyme systems A and α or α' are rendered inoperative by the drug. Clearly if only A or either of the enzymes α or α' are rendered inactive the drug response will be only partial. Change of the medium of phase I may affect the velocity of reactions of A, α and α' unequally and the rate of production of Y and thus of Z may show an increase and not a decrease.

Apart from direct action on the enzyme systems which includes possible reaction with the enzyme, co-enzyme or medium, the drug may affect the permeability of the phase II to the product Y or whilst affecting the enzyme system B can only obtain access to it by passage through the phase II. It is consequently important to investigate the separate mechanisms which come into operation under these different conditions.

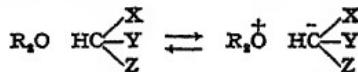
It is now well established that a number of drugs react directly on enzymes. Here we can distinguish between two distinct types of action: those drugs which react generally with proteins, e.g. colloidal silver or mercuric ions and complex mercurials resulting in the coagulation of the

protein and the loss of the necessary spatial configuration of the prosthetic group; and those drugs which are more specific to the enzyme and its carrier. Some quite tentative conclusions can be drawn concerning the specificity of such interactions. In many cases the interaction between drug and enzyme takes place at more than one point. Again, in general, one of these attachments possesses a larger interaction energy than the others. The "strong" attachment is in many cases a "hydrogen" bond. The electron donor group, *i.e.* the group which reacts with the acceptor hydrogen to form the bond may be situated either on the drug or on the substrate. In some cases the hydrogen bonding may be a distinct and separate phenomenon. One of the simplest of these reactions is to be noted in the staining of proteins by dyes. Thus in the case of the coloured wool dyes the hydrogen ion acceptor is the —COO^- group on the side chain of the wool fibre. The peculiar and strong adsorption of acids is due to the fact that in contrast to other ions the hydrogen ion combines with the —COO^- ion to yield a covalent product whilst the other cations remain ionic. The large coloured anion is then adsorbed on another site on the wool macromolecule. We shall return to discuss in more detail the interaction of these large anions but we may note in passing the significant fact that such ions are more strongly adsorbed than inorganic anions, even of greater charge, such as the SO_4^{2-} . Similar considerations apply to the "dyes" containing large organic cations (*e.g.* the acridine and tri-phenylmethane series).

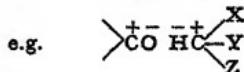
More generally the hydrogen bonding involves the whole of the molecule of the drug and not merely the indirect action due to adsorption of an electric charge.

We can identify many electron donating groups both in enzymes and drugs, thus the >O group in ethers, ketones, amides and esters, the $\equiv\text{N}$ group in aromatic amines and the $\equiv\text{S}$ group in sulphides.

The drug or substrate supplying the hydrogen to form the bond must have a particularly labile hydrogen. We have already noted the strong reactions of the free solvated hydrogen ions, we have also to consider especially the phenolic hydrogen group, and the rather unique —CO—NH— group where mutual reaction is possible since the group is both donor and acceptor in character. Weaker groups are found in the alcoholic hydroxyl and the weakest is the $\equiv\text{CH}$ group. The stability of the hydrogen bond can be regarded as determined in part either by the extent of resonance, possibly between the two forms



or by simple considerations of straight dipole interaction



Reactive $\equiv\text{CH}$ molecules will be found in those compounds in which suitable activating radicals are introduced into X, Y, and Z. It is interesting to note that the halogens are included in such groups. Chloroform is relatively highly reactive; the bond strength to a ketone being some 5.0 K. cal./gram. mol. Even greater values are found by fluorine substitution as in HCCl_2F .

In some cases two or more hydrogen bonds can be formed with the same reacting molecules giving, not only a stronger adhesion, but a great measure of spatial selectivity. I might mention the tanning agents, the α,β -dihydroxy stilbene derivatives, the α,ω -di-imidines and the p -amino-benzoic derivatives, as examples.

The case of chloroform is interesting since this drug does not affect appreciably the surface tension of water, being an exception to the Traube

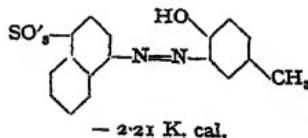
rule. The interaction of chloroform with water and alcohols is small since the mutual interaction between the water or alcohol molecules themselves is so great. We must consequently pay some attention to the competitive action of water in drug action and examine the methods by which this competition is overcome.

The non-polar, hydrocarbon or lipoid portion, both of the drug and of the substrate, provide the important secondary attachments by which this competitive action is reduced and by which also some degree of spatial specificity is introduced. In the adsorption of organic acids we have seen that the unique character of the hydrated proton in forming a covalent linkage with the $-COO'$ of the protein side chains results, from considerations of charge alone, in adsorption of the anion on a neighbouring site, preferably where the positive charge is situated. The organic anions are more strongly adsorbed than the inorganic ions even of higher valency and it is to the non-polar portions both of the anion and of the substrate, *i.e.* the side chains in a protein and the lipoid constituent in a lipo-protein, that this strong adsorption is due.

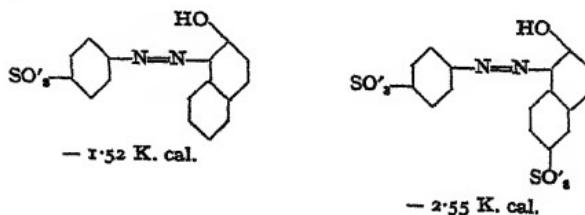
Recently Mr. Gilbert has been examining in my laboratory the free energies of adsorption on to proteins of a number of organic compounds of known constitution, and although this field of investigation is as yet in a very embryonic state some of the results he has obtained are very suggestive. Thus he finds:—

Anion.	Affinity in K. Cal. at 100° C.
	— 1.52
	— 0.19

From examination of a large number of anions it is found that the contribution to the interaction of a benzene ring can be expressed as effecting an average increment of 1.34 K. cal./ring. If we compare the above with the following value for



we find an increment of 0.7 K. cal. from which we may infer that adding a methyl group increases the affinity by 1.34 — 0.7 or ca. 0.64 K. cal./mol. CH_3 . We can in a similar manner examine the decrease in affinity caused by the introduction of a polar group. Thus Mr. Gilbert from examination of systems such as:—



finds that the introduction of further $-SO_3^-$ groups in spite of their negative charges brings about a reduction in intrinsic affinity in this case of ca. -1.03 K. cal./mol. SO_3^- . Multi substitution by $-SO_3^-$ groups always reduces the affinity although the extent of the reduction is dependent on the position of the substitution. Such substitutions may, however, be desirable in order to introduce solubility into the drug.

The spatial orientation of the apolar portions of the adsorbing molecules play an important part in the magnitude of the affinity of adsorption. This has been demonstrated in simple cases, such as cis and trans azobenzene on wool. A quantitative assessment of the "pattern" of apolar portions of a drug would seem to be capable of realisation.

The chromatographic method of purification which has proved so successful in preparative organic chemistry can be readily extended to serve as a most valuable method of examining and evaluating these affinities of adsorption of series of drugs in which progressive variation is made in their constitution.

We have noted in general the factor of drug accessibility has to be considered and this is depicted in the diagram by the introduction of the separate phase II, which may be regarded as a membrane which (in the diagram) must be permeable both to the product Y and any drug affecting the enzyme system B. The membrane is bounded by two interfaces, and the nature of the actions which can occur at interfaces are thus of fundamental importance. Dr. Schulman has dealt with several aspects of these reactions on which we have been engaged for many years. I will in consequence merely make a few comments on this point. The phenomenon of monolayer penetration where on injection of a reactant underneath a monolayer a reaction occurs in the sense that the injected molecules penetrate the monolayer and form a one-one complex with a resulting increase in area or in pressure of the monolayer, is only noted where there is both head group interaction frequently, as Dr. Alexander has shown, of the hydrogen bond type and, in addition, adlineation and interaction between the tails or non-polar portions of the two reactants. This represents a modification of both the Traube and Overton concepts. Furthermore, the mixed monolayer may, in several cases, be displaced, "peptised" or "detected" from the surface by the added reactant and driven into the substrate as a complex, e.g. a lipo-protein. In view of the completeness of this type of reaction it seems improbable that the phase II can ever consist of a single monolayer and in consequence natural membranes must be thicker than a monolayer.

Further evidence is found to support this view, since monolayers and even multilayers of some thickness of proteins do not apparently offer any resistance to the flow of ions through them. These experiments are worth extending to include monolayers and multilayers of the lipoids and lipo-proteins concerning the permeability of which our information is much less complete. Experiments on cholesterol protein monolayers support the view that the cholesterol is anchored to the protein at specific points and that the injection underneath such a lipo-protein monolayer of both protein penetrating and lipoid penetrating reagents results in interaction whereas under pure protein or pure lipoid monolayers the reactions are selective.

These complexes formed by head and tail interaction are clearly important in many biological processes; they may act as carriers for otherwise non- or difficultly-transportable reactants; they may remove a reactant from the system or may displace a reactant from a substrate.

The evidence from monolayer properties and behaviour suggests that phase II must in general be considerably thicker than a monolayer, it must consist of a real membrane and contain lipo-protein. The fact that cholesterol has definite points of attachments to a protein monolayer leads one to infer that the lipo-protein membrane possesses some definite structure laminated in character; that this structure is always as uniform

as the investigations of Schmitt and his co-workers on the nerve myelin sheath suggest is unlikely; but it is clear that such a composite membrane will be permeable to polar, apolar, and heteropolar molecules, the relative permeability of each type being dependent on the phase volume relation and orientation factor of the two constituents. Such a view suggests that the properties of the membrane as far as permeability are concerned are comparable to those which a mosaic membrane would possess. Evidently, either phase can be extended by suitable solvents resulting in the increased permeability for lipoids or non-lipoids as the case may be and passage which can be termed interfacial in which both the protein and lipid phases participate can be envisaged. Several aspects of this effect are dealt with by Dr. Hurst who considers, *inter alia*, the mode of action of carriers and adjuvants in insecticides.

CHEMICAL CONSTITUTION AND PHARMACOLOGICAL ACTION.

By H. R. ING.

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The first systematic study of the relations between chemical constitution and pharmacological action was made by Crum Brown and Fraser¹ in their classical work on the metho-salts of alkaloids. They postulated that the physiological action Φ of a drug was a function of its chemical constitution C , in which term they included both the structure and the energy relations of the molecule; they even put this relation into mathematical form: $\Phi = f(C)$. This extreme physicochemical view would hardly be accepted to-day since it neglects the highly complicated nature of the physiological situation in drug action. The importance of the physiological situation was stressed by Ehrlich, and although Ehrlich's so-called side-chain theory is now regarded as too simple and too rigid, modern views are more closely akin to his general theory of drug action than to the ideas of Crum Brown and Fraser. Ehrlich would have classified drugs in terms of their capacity to combine with protoplasmic constituents rather than pharmacological actions in terms of chemical structure.

Modern views are both less ambitious and less precise than those of Ehrlich; they may be summarised in two rather vague principles: (1) Similarity of chemical structure in drugs may be expected to involve similarity of pharmacological action; this is the working hypothesis of the organic chemist; and (2) the action of a drug depends upon the way in which it impinges on the normal chemical mechanisms of the tissues. Both principles are to be found in Ehrlich's writings.

A modern version of Ehrlich's general theory of drug action has been put forward and critically examined by A. J. Clark² in his "General Pharmacology". Clark assumes that drug molecules combine with specific receptor substances, which in most cases appear to be situated on cell surfaces; the physiological action of the drug is regarded as occurring subsequently to, but in consequence of, this drug-receptor combination. The nature of the drug-receptor combination is unknown, but as it is often reversible, it is regarded as analogous to the enzyme-substrate combination assumed to precede enzyme activity.

¹ Crum Brown and Fraser, *Trans. Roy. Soc., Edinb.*, 1868-9, 25, 151.

² Clark, "General Pharmacology," in Heffter's *Handbuch der experimentellen Pharmakologie*, 1937.

In his examination of the evidence Clark concluded "that a somewhat surprisingly large proportion of the more accurate quantitative data can be interpreted as the expression of a chemical reaction between the drug and specific receptors" and consequently it may be of value to consider to what extent the theory can be used to interpret the data on the relations between chemical constitution and pharmacological action; it will be the purpose of this article to make the attempt.

It may be noted first that the receptor theory provides an intellectual link, otherwise missing, between the diverse concepts of structure and action; ideally the relation to be sought is one between the structures of the drug and receptor molecules. The first general principle mentioned above should be that similarity of chemical structure in drugs may be expected to involve combination with the same receptors. It is our complete ignorance of the chemical nature of the hypothetical receptors which forces us to look for relations between the structure of drug molecules and the physiological effects presumed to flow from the drug-receptor combination. It will also be noticed that the receptor theory only pushes the problem of drug action a stage further back since it provides no explanation of the physiological efficacy of the drug-receptor combination. At the same time the theory has solid advantages; it offers the possibility of relating the structure of drugs to their action in chemical terms, it brings drug action into line with the theory of chemical transmission and draws an analogy between drug action and enzyme action which may well prove fruitful to the study of both.

Pharmacodynamic Groups.—In devising synthetic drugs the organic chemist frequently uses a known drug as a model and, relying on the principle that similarity of structure may involve similarity of action, tries to discover what structural features must be retained in order to preserve the typical activity. The very large body of work on these lines has made it clear that the pharmacological properties of drug molecules can frequently be shown to depend upon particular structural features, which may be regarded as pharmacodynamic structures or groups. The evidence for such groups is of three main types:

(1) Alteration or removal of particular groups in a drug molecule may lead to drastic diminution or even complete disappearance of a particular pharmacological response; e.g. the integrity of the unsaturated lactone ring in the cardiac glycosides is essential for the retention of the typical action on the heart and as Ehrlich discovered the benzoyl group is essential to the local anaesthetic action of cocaine.

(2) Conversely, alterations in structure which leave the typical action of a drug molecule unchanged reveal inessential structural features, e.g. the carbomethoxy group in cocaine and the detailed structure of the aliphatic side-chain in vitamin D.

(3) The synthesis of new structures based on evidence of types (1) and (2) has supplied convincing evidence of the existence of pharmacodynamic groups in certain classes of drugs; e.g. it can be predicted with reasonable certainty that molecules embodying the structural unit, $R_1R_2N \cdot (\bar{C})_n \cdot O \cdot CO \cdot Ph$ where $n = 2, 3, \dots$, will possess local anaesthetic properties. A striking illustration is provided by the observation that the attachment of a β -benzoylethyl or a γ -benzoylpropyl group to the secondary nitrogen atom of the alkaloid cytisine confers considerable local anaesthetic properties on the new molecule, while the powerful nicotine-like actions of cytisine itself completely disappear.*

Pharmacodynamic groups have also been identified in atropine and physostigmine and synthetic substitutes for these drugs synthesised. With a few exceptions, Crum Brown and Fraser's original generalisation that quaternary ammonium salts, and onium salts in general, exert a

* Ing and Patel, *J. Pharmacol.*, 1937, 59, 401.

curare-like action remains true; the onium cation must be regarded as the first pharmacodynamic group to be discovered.

Pharmacodynamic groups are the lineal descendants of Ehrlich's anæsthophore groups, toxophore groups, etc., and their occurrence finds a simple interpretation in terms of the receptor theory; the receptors, which must be regarded as adapted to some normal physiological process, will combine with and respond to strictly limited types of molecules. The more highly selective the action of the drug the more probable becomes the hypothesis of specialised receptors which respond only to molecules with precisely defined structural features. Certain classes of drugs, such as autonomic drugs and cardiac glycosides, exert a selective action comparable only with that of hormones and chemical transmitters and to account for the action of the latter some form of receptor theory appears to be necessary.

Drugs of Diverse Structure and Similar Pharmacological Action.

Although certain pharmacodynamic groups may be established, similar pharmacological properties may be shown by drugs of quite different structure; thus local anaesthetic properties are displayed by drugs which do not conform to the dialkylaminoalkyl benzoate type, e.g. benzyl alcohol, quinine and certain anti-malarials of the plasmoquin type.⁴ Such examples do not invalidate the relations established between structure and action among local anaesthetics of the dialkylaminoalkyl benzoate type so long as it is admitted that local anaesthesia may be achieved by a variety of mechanisms. That the same physiological result can be achieved by different mechanisms is well established, e.g. the dilatation of the pupil by atropine and by ephedrine and the parasympathetic actions of acetylcholine and eserine, and consequently the assumption that the same physiological result may be produced by different mechanisms can often be made without impropriety. The diversity of chemical antisepsics is not surprising; the living cell is an extremely complex system and a drug which inhibits any one of a (probably large) number of vital chemical processes may be expected to lead to the death of the cell. Moreover, the cell has only a limited number of ways of responding to stimuli; it can only display its normal types of activity in increased or diminished intensity. Since the normal activities of a cell certainly involve a large number of consecutive chemical reactions, drugs may attack different points in this chain of chemical events and yet produce the same end result.

The difficulty only becomes acute when we consider groups of drugs of diverse structure which possess similar and highly selective actions occurring at well-defined sites in the body. The parasympathomimetic drugs, acetylcholine, muscarine, physostigmine and pilocarpine constitute such a group. Here again, more detailed pharmacological analysis may demonstrate, as has been done for physostigmine, that different mechanisms are involved.

Closer definitions of similarity and diversity of structure are made necessary by the receptor theory, and in this connection more consideration should be given to changes in physical properties accompanying structural changes. In their classical work on sympathomimetic amines, Barger and Dale⁵ observed the qualitative similarity in action of iso-amyamine and adrenaline; on chemical grounds it is difficult to imagine that a simple aliphatic amine can form an effective combination with the same receptors as the more complex amphoteric substance adrenaline;

⁴ E.g., δ (γ -diethylamino- $\beta\beta$ -dimethylpropylamino)-6-ethoxyquinoline; Bovet, *Arch. internat. Pharm. Therap.*, 1931, 41, 103.

⁵ Barger and Dale, *J. Physiol.*, 1930, 41, 19.

and when the great difference in the intensity of the actions of these two substances is borne in mind, the view that they combine effectively with the same receptors involves a surprising discrepancy between the qualitative and the quantitative discrimination of the receptors. Attempts to relate structure and action among such physicochemically dissimilar drugs is bound to be fruitless; even ephedrine, which has a greater structural resemblance to adrenaline than isoamylamine, must be regarded as physicochemically dissimilar. These "sympathetic" amines are now classified by some workers as sympatheticotropic drugs, which are thought to form effective combinations with the adrenaline receptors and which have amphoteric structures closely related to adrenaline, and sympathomimetic drugs which are less closely related to adrenaline in structure and physical properties and are thought to achieve "sympathetic" action by other mechanisms.⁶ The view that such amines as isoamylamine and ephedrine are on physicochemical grounds unlikely to form effective combinations with the adrenaline receptors does not rule out the possibility of their forming ineffective combinations; ephedrine is known to inhibit amine oxidase, which can catalyse the oxidation of adrenaline, and also to antagonise adrenaline (see below).

Another example of drugs of diverse structure and similar pharmacological action is provided by the aliphatic narcotics, which include a large variety of structural types, e.g. hydrocarbons, alcohols, ethers, amides, urethanes, sulphones, etc. These drugs appear to achieve their effect by modifying the physicochemical conditions of cells, and their action is regarded as depending not on pharmacodynamic groups but on certain physical properties shared by all classes of these compounds.

Drugs of Similar Structure and Diverse Pharmacological Action.

The observation that the action of a particular drug may be antagonised by another drug of similar structure occurs fairly frequently and finds a simple interpretation in terms of the receptor theory. If it be assumed that both drugs combine with the same receptors, but that only one of the drug-receptor combinations is physiologically effective, then the ineffective drug-receptor combination will reduce the activity of the effective drug by limiting the number of free receptors available to it. This theory involves the assumption that the structural requirements of the receptor for combination with a drug are less exacting than those for the production of the characteristic physiological response. There is considerable justification for this assumption because the inhibition of enzymes by compounds structurally related to their normal substrates is well established. Thus, ephedrine inhibits the oxidation of adrenaline by amine oxidase *in vitro*,⁷ presumably it can combine with the enzyme, but unlike adrenaline it is not oxidised. Similarly, ephedrine has been found to antagonise a variety of the actions of adrenaline, e.g. on the dog's blood pressure, rabbit's intestine, etc.,⁸ and these results can be accounted for by the assumption that ephedrine combines with the adrenaline receptors but that the combination is physiologically ineffective.

An even more striking example was studied by Raventos,⁹ who found that the higher members of the homologous series of cations $R \cdot NMe_2^+$ ($R = C_7H_{15}, C_8H_{17}, C_{10}H_{23}$) antagonised the muscarine-like action of the lower members ($R = CH_3, C_2H_5, C_3H_7, C_4H_9, C_5H_{11}$) on the frog's auricle.

⁶ Cf. Gaddum and Kwiatkowski, *J. Physiol.*, 1938, 94, 87.

⁷ Blashko, Richter and Schlossmann, *Biochem. J.*, 1937, 31, 2187.

⁸ For references, see Gaddum and Kwiatkowski, *loc. cit.*⁶.

⁹ Clark and Raventos, *Quart. J. exp. Physiol.*, 1937, 26, 375; Raventos, *ibid.*, 1938, 27, 99.

The lower members acted additively with acetylcholine and were antagonised by atropine; the higher members antagonised both acetylcholine and the lower members. Moreover, the doses of a higher member (e.g. $\text{C}_8\text{H}_11\overset{+}{\text{NMe}_3}$) required to reduce the effect of equiactive doses of $\text{Me}_2\overset{+}{\text{N}}$ and acetylcholine by a given amount were similar, although equiactive doses of $\text{Me}_2\overset{+}{\text{N}}$ and acetylcholine were in the ratio 1000:1. These facts can be explained by the assumption that all the cations RNMe_3^+ combine with the acetylcholine receptors but that the combination is physiologically ineffective for the higher members.

It is interesting to note that the first recorded example of onium salts antagonising acetylcholine was only recognised as such in recent years; it is the curariform action of onium salts¹⁰ discovered by Crum Brown and Fraser.

The occurrence of enzyme inhibition by a competitor of structure related to the normal substrate has been recognised recently as of great importance in bacterial chemotherapy. Since the original observation of the mutual antagonism of *p*-aminobenzoic acid and sulphanilamide *in vitro*¹¹ and *in vivo*,¹² several other pairs of mutually antagonistic substances in bacterial metabolism have been recorded, e.g. nicotinic acid and pyridine-3-sulphonic acid,¹³ pantothenic acid and pantoyltaurine,¹⁴ etc., and there is little doubt that other examples will be discovered.

Quantitative Considerations.

The influence of structural changes on the intensity of drug action provides the most difficult problems in any attempt to relate structure and action. Knowledge in this field is handicapped by the difficulty of measuring most pharmacological actions accurately and is complicated by the use of different methods by different authors.

It may be of value at the outset to consider how differences in intensity of action are to be interpreted in terms of the receptor theory. The intensity of a drug action will on this theory depend at any moment on the number of drug-receptor combinations, and for any given concentration of drug, this number will be determined by the ease with which the drug-receptor combination is formed. For a reversible drug reaction the relation between concentration c and action y should follow a rectangular hyperbola, $Kc = y/100 - y$, where y = percentage of the maximum possible action. Clark¹⁵ has discussed the applicability of this equation in detail; a similar equation holds for the reversible inhibition of enzymes by metals¹⁶ and dyestuffs.¹⁷

The drug-receptor combination must be regarded as leading to an all-or-none type of response; if this were not true, a weaker drug would partially antagonise a stronger when both were used together. Raventos¹⁸ found that this did not occur with combinations of acetylcholine and onium cations such as $\text{Bu}_3\overset{+}{\text{NMe}_3}$ on the frog's heart; although $\text{Bu}_3\overset{+}{\text{NMe}_3}$ had only about a hundredth of the activity of acetylcholine, it acted additively with acetylcholine when combinations of the two drugs were used. This result implies that equal intensities of action involve equal

¹⁰ Ing, *Physiol. Rev.*, 1936, 16, 527.

¹¹ Woods, *Brit. J. exp. Path.*, 1940, 21, 74.

¹² Selbie, *ibid.*, p. 90.

¹³ McIlwain, *ibid.*, p. 136.

¹⁴ Snell, *J. Biol. Chem.*, 1941, 139, 975; 141, 121; Kuhn, Wieland and Müller, *Ber. dtsch. chem. Ges.*, 1941, 74, 1605; McIlwain, *Biochem. J.*, 1942, 36, 417.

¹⁵ Myrbäck, *Hoppe-Seyler's Z.*, 1926, 158, 160.

¹⁶ Quastel and Yates, *Enzymologia*, 1936, 1, 60.

numbers of combinations of the different drug molecules with the receptors, but the concentrations needed to produce equal numbers of combinations may vary over a very wide range.

Although the individual reaction between drug molecule and receptor must be regarded as producing an all-or-none response, the total physiological effect observed will usually appear as a graded response because of the large number of receptors involved.

The ease of combination of a drug with specific receptors may be expected to depend upon a large number of factors, e.g. stereochemical configuration, size and shape of the molecule and the disposition of the pharmacodynamic groups, the nature of acidic and basic groups, etc.

Stereochemical Specificity.

Stereoisomeric drugs often differ in the intensity of their action. The most striking examples are those optical enantiomorphs, e.g. *L*-adrenaline and *L*-hyoscyamine, which are twice as active as the corresponding racemic compounds. The subject was thoroughly investigated by Cushny,¹⁷ who argued that a clear differentiation in the activities of optical enantiomorphs indicated that the drug combined chemically with an optically active tissue constituent and that the different activities were to be ascribed to different physicochemical properties in the compounds so formed. Other factors might also be involved, e.g. more rapid destruction of one enantiomorph by enzymic action in the body.

Cushny's views are difficult to reconcile with the receptor theory because he assumed that the intensity of the physiological action was determined by the nature of the combinations which each enantiomorph formed with the same tissue constituent; but on the receptor theory both enantiomorphs must form equally effective combinations with the receptors. If this were not so, the less active enantiomorph would partially antagonise the more active when both were present. Experiment shows, however, that optical enantiomorphs act additively when used in combination; thus Cushny¹⁷ found that *L*-hyoscyamine was 15-20 times as active as *d*-hyoscyamine on the dog's salivary gland and twice as active as atropine; *L*-hyoscine was 16-18 times as active as *d*-hyoscine and twice as active as *dl*-hyoscine; *L*-adrenaline was 12-15 times as active as *d*-adrenaline in its vasoconstrictor action and twice as active as *dl*-adrenaline. These results agree with the requirements of the receptor theory, but it must be admitted that the quantitative data are scanty and a closer examination of the additive properties of optical enantiomorphs is desirable.

On the receptor theory the difference in activity of optical enantiomorphs will depend upon the ease with which each isomer combines with the receptors. This conclusion is remarkable but appears to be inescapable if they act additively. On the other hand, the view that the ease of combination with receptors is determined by stereochemical configuration appears to be reasonable in the case of stereoisomers which are not optical antipodes.

Homologous Series.

A study of the activities of homologous drugs is of interest because the structural changes involved are of the simplest character. Two main types may be distinguished: (1) Homologous series in which the activity increases regularly as the series is ascended, e.g. the aliphatic narcotics, and (2) series in which the activity increases to a maximum and then declines.

¹⁷ Cushny, *Biological Relations of Optically Isomeric Substances*, Baltimore, 1926.

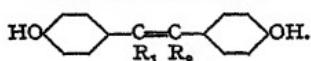
(1) When the logarithm of the narcotic concentration of homologous compounds is plotted against the number of carbon atoms a linear relation is obtained. Ferguson¹⁸ has pointed out that with such a series all the physical properties like solubility, vapour pressure, surface tension, etc., which depend upon a distribution between two phases, also change logarithmically with the number of carbon atoms. It is generally agreed that narcotic activity depends upon a distribution equilibrium between the medium bathing the cells and the biophase (whatever it may be) in which the drug has its effect, but the prolonged controversy between the differential solubility and the adsorption theories of narcosis reflects the difficulty of deciding between properties which vary from one member to the next in exactly the same way. Which physical property determines narcotic activity cannot be decided by consideration of the relations between activity and physical properties in one series; the effects produced by members of different homologous series must be correlated.¹⁹ This problem still awaits solution.

The logarithmic decrease in narcotic concentration in a homologous series proceeds until a member is reached which exerts the same narcotic effect as the lower members only when present as a saturated vapour or solution; beyond this member, further members will be inactive or only feebly active.

(2) The commonest type of variation within a homologous series is that the activity rises to a maximum as the series is ascended and then declines. A striking example is provided by the oestrogenic activity of the 4:4'-dihydroxy-dialkyl stilbenes,²⁰ which show maximum activity for the diethyl member (Table I).

Similar results have been observed with alkyl phenols and cresols,²¹ alkyl resorcinols,²² alkyl hydrocupreines,²³ etc.; among antiseptics of this type the position of the maximum in the series may vary with the type of organism used.

TABLE I
OESTROGENIC ACTIVITY OF DIHYDROXY-DIALKYL STILBENES.



R ₁ .		Rate Units Per Gram.
H	H	140
H	Et	5,000
Me	Me	40,000
Me	Et	1,000,000
Et	Et	3,000,000
Et	nPr	300,000
nPr	nPr	50,000
isoPr	isoPr	20,000
nBu	nBu	5,000

Barger²⁴ argued that the activity in such series must represent the summation of two opposing effects, which must be physical in character; thus, in the aliphatic primary amines, which show maximum pressor action at the n-hexyl member,⁵ he suggested that the two opposing effects might be the decline in basicity and the increase in surface tension as the series is ascended. The view that the ease of formation of the drug-receptor combination depends upon an optimal balance of two opposing effects is attractive, but it is difficult to see how it could be tested.

Barger also suggested that when two pharmacodynamic groups in a drug molecule are separated by an alkyl chain, the length of the chain may determine the ease of combination with receptors, e.g. in local

¹⁸ Ferguson, *Proc. Roy. Soc., B*, 1939, 127, 387.

¹⁹ Meyer, *Trans. Faraday Soc.*, 1937, 33, 1067.

²⁰ Dodds, Goldberg, Lawson and Robinson, *Proc. Roy. Soc. B*, 1939, 127, 142.

²¹ Coulthard, Marshall and Pymann, *J. Chem. Soc.*, 1930, 280.

²² Leonard, *J. Amer. Med. Ass.*, 1924, 83, 2005.

²³ Morgenroth, *Biochem. Z.*, 1914, II.

²⁴ Barger, *Some Applications of Organic Chemistry to Biology and Medicine*, New York, 1930.

anaesthetics, maximum activity is usually shown by members in which the dialkylamino and benzoyl groups are separated by a three-carbon chain.

In a recent study of the bacteriostatic properties of polymethylene diamines, diaminides, diguanidines and di-isothioureas Fuller²⁵ found that maximal activity was usually reached when the polymethylene chain had 14 to 18 carbon atoms. Interpretation of the results is, however, made difficult by his observation that the position of the maximum in all series except the di-isothioureas varied with the medium; the maximum occurred at a shorter chain length for organisms in serum than for the same organisms in broth.

The assumption that any homologous series of drugs will show maximum activity for one member is a useful working hypothesis for the organic chemist but not all homologous series display the satisfactory regularity of the examples already quoted; thus the relative activities of homologous choline esters exhibit remarkable relations (Table II).

TABLE II
RELATIVE POTENCIES PER MOLECULE OF CHOLINE ESTERS.²⁶
(Acetylcholine = 100 in each case.)

Ester.	Rabbit Intestine.	Frog's Rectus Abdominis.		Leech.	Rabbit's Blood Pressure.
		Without Eserine.	After Eserine.		
Acetyl . . .	100	100	100	100	100
Propionyl . . .	3	550	450	45	4
Butyryl . . .	0.24	90	115	90	0
Valeryl . . .	0.20	25	30	0.9	0

Homologous series are also known in which one member (other than the first) has minimum activity; e.g. minimum curariform activity occurs for R = Et in the series R₄N, R₄P and RNMe₃, where R = Me, Et, Pr and Bu. This effect is not caused by any intrinsic properties of the ethyl group because in the arsonium series R₄As the least active member is Me₄As, and Et₃As is equal in activity to Me₄N; also in the alkylquinolinium series the metho-salts are less active than the etho-salts.²⁷ These examples are peculiarly puzzling because among simple onium salts the curariform activity is remarkably independent of detailed chemical structure and appears to depend primarily on the ionic character of onium cations.¹⁰

Conclusion.

The receptor theory provides a useful intellectual framework for the consideration of the qualitative aspects of the problems presented by the structure and action of drugs; in particular it is the only satisfactory means of accounting for the antagonism of structurally similar drugs. It is less useful for the consideration of the quantitative aspects of the subject because "ease of combination with the receptors" is too vague a concept when the structural requirements of the receptors are unknown.

²⁵ Fuller, *Biochem. J.*, 1942, 36, 548.

²⁶ Chang and Gaddum, *J. Physiol.*, 1933, 79, 255.

²⁷ Ing and Wright, *Proc. Roy. Soc. B*, 1933, 114, 50.

It is possible in certain cases to predict the kind of drug action which will result from structural changes in a drug molecule, but the changes in intensity of action resulting from even the most trivial alterations in structure cannot be predicted.

The receptors must be regarded as highly complex, and specialised receptors may differ in different tissues. Some such assumption appears to be necessary to account for the fact that the qualitative and quantitative actions of drugs differ in different tissues; e.g. atropine is the best known antagonist of acetylcholine but it does not antagonise acetylcholine in mammalian voluntary muscle; Me_4N^+ acts additively with acetylcholine on the frog's heart but antagonises acetylcholine in voluntary muscle, while Table II illustrates the quantitative irregularity of choline esters in different tissues. Facts of this kind led Clark²⁸ to conclude that every cell-drug system was a law unto itself. It is, however, a sound rule in studies of the structure and action of drugs to confine attention to one pharmacological action in one tissue and not to expect relations so observed to be necessarily applicable to other actions in other tissues.

It has been tacitly assumed throughout this article that all the receptors in a given tissue are equally accessible to drugs and equally effective in the physiological sense. Both assumptions are rather improbable; it is more likely that the receptors are subject to individual variation. If this be assumed, a reconciliation might be effected between Clark's view that concentration-action curves express the relation between the concentration of the drug and the uptake by the receptors and Shackell's²⁹ view that they express the relation between the uptake of the drug and its effect on a mixed population of cells.³⁰

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Dr. Ing (*Oxford*), in introducing his paper, said: In his Introductory Address Sir Henry Dale criticised the receptor theory on the ground that it added nothing to our knowledge, but was only an alternative way of describing the well-established pharmacological facts. The theory is not meant to be other than an alternative method of describing the known facts, which, however, is thought to have the additional advantages of suggesting new approaches to the problems and of providing a much-needed intellectual link between the diverse concepts of chemical structure and pharmacological action.

In quoting the selective and similar stimulant properties of tetra-methyl-ammonium salts and the natural alkaloids, nicotine, cytisine and lobeline, Sir Henry Dale has mentioned one of the most puzzling examples of diverse structure and similar physiological action, but his assumption that on the receptor theory all these drugs must be thought to have affinity for the same chemoreceptors is not necessarily well founded. The more selective a drug action is, the more probable is the assumption that the drug acts in virtue of an affinity for specialised receptors and the less likely that such receptors will combine with drugs of diverse structure. It is not necessary to assume that a highly selective action elicited by a variety of drugs always implies combination with the same receptors, as the well-known example of acetylcholine and eserine illustrates. It may prove to be a merit of the receptor theory that it draws attention to problems, like that quoted by Sir Henry Dale, where closer pharmacological analysis is needed.

²⁸ *Loc. cit.*,² pp. 190-199.

²⁹ Shackell, *J. Gen. Physiol.*, 1923, 5, 783.

³⁰ Cf. Gaddum, *Proc. Roy. Soc. B*, 1937, 121, 598.

Mrs. Catherine Le Fèvre (London) (communicated): For a few years prior to the outbreak of war, Dr. R. J. W. Le Fèvre and I were investigating at University College, London, the Kerr Electro-Optical properties of organic substances in vapour and solution form. From the results obtained from our experiments, in conjunction with results we also obtained from the measurements of dielectric constants which yielded dipole moment data, we have been able to calculate the optical polarisability tensor ellipsoids of these substances. For the solvent state, only an approximate of the true polarisability of a molecule along the three directions—maximum, minimum, and the direction perpendicular to these two—of polarisability which define the tensor ellipsoid, can, of course, be ascertained. But in the investigation of substances in an homologous series dissolved in a solvent of low Kerr constant, it should be possible to obtain a good qualitative picture, which might throw considerable light on why there appear to be the two main types observed in the activities of homologous drugs. A series, e.g. the dihydroxy dialkyl stilbenes in which the activity increases to a maximum and then declines, might possibly be explained by a change in geometric structure due to buckling of the molecule, this would easily be detected by experiments on the Kerr effect.

Further, divergences in the optical polarisability tensor ellipsoids, which conforms to the geometric shapes of the molecules, in the choline ester series might again throw light on the anomalous relative activities observed, yielding ultimately to information concerning the structural requirements of the receptors.

W./Cdr. Le Fèvre is on active service in the Far East, but he would wish to join me in offering Dr. Ing, through our own investigations post war, any help that we might be able to give in relating polarisability and pharmacological activity.

Dr. H. R. Ing, in reply, said: The measurement of many physical properties involves techniques unfamiliar to the organic chemist and the kind of co-operation between organic and physical chemists which Mrs. Le Fèvre has suggested seems to me to be the best way to advance the subject.

Dr. D. B. Taylor (London) said: The consideration of the active group of an enzyme as a "receptor" sheds considerable light on the relationship between drug structure and action. For example, the very large effects produced by polar substitution in certain organic molecules on the velocity of their hydrolysis by specific enzymes suggests that even the polar contribution of hydrocarbon side chains may be of importance.

Dr. D. D. Eley (Cambridge) (communicated): Throughout the Discussion attention has been focussed upon the importance of Van der Waal's forces and related bonds, as distinct from the covalent bond. In support of this view, one contributor in the Discussion has stressed the reversible nature of the drug-receptor combination. While not wishing to contradict this view-point, I would like to point out that the possibilities of covalent bond formation should not be neglected. The formation of covalent bonds between drug and receptor may in principle be expected to introduce more profound changes in the receptor (e.g. enzyme molecule) than the mere formation of a Van der Waal's bond, since in the former case the whole pattern of the molecule may be expected to be altered. Of course, the formation of the Van der Waal's complex may be a necessary first step to covalent bond formation, but by itself less likely to introduce profound chemical changes in the enzyme molecule, or other receptor. Secondly, while it is true that many of the well-known reactions of chemistry (such as the $H_2 + I_2$ reaction), in which a rearrangement of covalent bonds occurs, only takes place at high temperatures because of the high activation energy involved, this is by no means universally the case. I would quote the well-known reaction between oxygen and haemoglobin, thoroughly studied by Hartridge and Roughton. This occurs rapidly and reversibly at room temperature, and one of the early theories assumed it to be a

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physical adsorption of the oxygen upon the haemoglobin colloid. However, during the last twenty years much evidence has accumulated to show that this reaction involves the formation of chemical bonds between the oxygen and the Fe in the haemoglobin. Recently, L. Pauling and collaborators have shown that the paramagnetic moment of both the haemoglobin and the oxygen disappear in the reaction to give a diamagnetic oxyhaemoglobin, a fact which indicates an extensive rearrangement of electron levels in the reaction. The reasons for the rapidity of this reaction are still by no means clear, but a few years ago Polanyi and Evans showed in principle how quantum mechanical resonance, that may occur in molecules containing conjugated double bonds, can work so as to lower the activation energy of association reactions. There are also other theoretical mechanisms which may be visualised to explain the rapidity of reactions between proteins, etc., but the need at the present moment is more for an extensive study of a suitably chosen, clearly defined case.

Dr. H. Hurst (Cambridge) said : The concepts of Ehrlich and Clark that quantitative pharmacological data may be expressed in terms of chemical interaction between drugs and specific receptors, and that drug fixation at these receptors is measured by concentration-action curves are open to the following criticisms :

(1) Owing to the disturbing influence of selective adsorption at functional interfaces in the system, the active concentration of a drug measured in a bulk external drug phase may be much smaller than the actual concentration at the *primary* site of action, i.e. the common drug phase/biological phase interface.

(2) The receptor theory is only valid when it is known that drug access is not influenced by a selective diffusion process. The antagonism of drugs which are structurally similar may be partially an expression of molecular interaction or competition for the lipo-protein receptors in a bounding biophase where drug mobility is influenced by "pharmacodynamic" groups and also by less specific hydrocarbon or fat-soluble portions of the drug molecules.

(3) Selective drug access may also account for the irregularity shown by the positions of maximum activity in different homologous series. With increase in the van der Waals' interaction between the hydrocarbon portions of the drug molecules and the lipoid components of the lipo-protein mosaic substrate, two factors influence two-dimensional drug mobility along the functional interfaces of the bounding substrate : (i) an increase in the rate of drug access owing to "carrier action" of the drug molecules which is associated with a decrease in "functional viscosity" of the lipoid loci ; and (ii) a decrease in the rate of drug access owing to the establishment of a *balance* between the polar and non-polar interactions of the drug molecules with the protein and lipoid components of the biological substrate. The establishment of this balance would tend to favour adsorption at the outer surface or layer of the diffusion barrier. The position in a homologous series of drugs at which the competing factors (i) and (ii) become respectively dominant will depend, not only on the stereochemical configurations of the drug molecules, but also on the physico-chemical properties of the acceptor groups in the particular biological tissue or organism. The magnitude and irregularity of the variation in relative activity of the choline esters with increase in chain length can hardly be attributed to corresponding differences in specific drug-receptor combinations based on the somewhat static conceptions of chemical affinity, and may be more readily interpreted in terms of selective diffusion, which varies enormously according to the particular biological component in the system. Further evidence in support of this theory is provided by the fact that the position of maximum activity in a series varies with the carrier medium, suggesting that carrier activity plays an important part in modifying the functional susceptibility of the biological system.

Dr. H. R. Ing, in reply, said : The type of drug-receptor combination envisaged in my paper need not be restricted to reactions involving principal valencies, such as salt formation and condensation reactions ; such reactions probably do occur, e.g. the reversible formation of thiocarsinates by arsenoxides and thiol compounds, but partial valencies may frequently be involved as well as, or even without, principal valencies. Most reversible drug reactions probably occur at cell surfaces, and for such reactions the drug-receptor combination seems to be most usefully regarded as a two-dimensional combination at an interface ; some types of drug specificity seem inexplicable except in terms of surface reactions such as Prof. Rideal has enumerated in his paper. It may be noted in this connection that the nearest analogy to the differential pharmacological activity of some optical enantiomorphs is the differential adsorption of some dia-stereoisomerides.

The importance of the physical properties of drugs has been stressed in several papers submitted to this Discussion, but it appears that some clarification of the significance of such properties to theories of drug action is needed. I am in general agreement with Sir Henry Dale's remarks on this subject in his Introductory Address. What appears to be needed is the same sort of correlation of physical properties with pharmacological activity as the organic chemist has achieved for the structural features of some classes of drugs. It is usually found that several functional groups or structural units must be combined in a drug molecule before a particular pharmacological response can be elicited. In the same way it is probable that drug actions depend upon a combination of physical properties ; it is unlikely that such complex phenomena as drug actions will be found to depend upon one physical property only, however apparently apt to biological situations the property may appear.

CHEMICAL STRUCTURE OF ARSENICALS AND DRUG RESISTANCE OF TRYPANOSOMES.¹

By HAROLD KING.

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The science of chemotherapy was founded by Ehrlich, and in this science one of Ehrlich's most important discoveries was that of drug-fastness or -resistance. This latter subject he developed experimentally and theoretically, and in an inspired manner he adorned the subject by coining technical terms as the vehicle for his thoughts.

Browning, Franke and Roehl,² working in Ehrlich's laboratory, were the first to produce drug-resistant strains of trypanosomes, the phenomenon being observed initially with parafuchsin. It was soon shown, however, that drug-resistance could be produced with an arsenical, atoxyl. Such an atoxyl-resistant strain was also resistant to a great number of substituted derivatives of phenylarsonic acid,³ but infections in mice with this strain could be cured by arsenophenylglycine. Other arsenicals containing the acetic acid radicle contained in arsenophenylglycine, e.g. arsenophenylthioglycollic and arsenophenoxyacetic acid, had also the power of curing infections of atoxyl-resistant trypanosomes.^{4, 5} Ehrlich and his collaborators made the further important observation that atoxyl-resistant

¹ King and Strangeways, *Ann. Trop. Med. Parasit.*, 1942, 36, 47.

² Ehrlich, *Ber. Klin. Woch.*, 1907, 44, 233, 341.

³ Ehrlich, *Ber. deutsch. Chem. Ges.*, 1909, 42, 36.

⁴ Ehrlich, *Arch. Schiffs. Trop.-Hyg.*, 1909, 13; Beiheft, 6, 91.

⁵ Ehrlich, *Zeit. Angew. Chem.*, 1910, 23, 2.

strains were also resistant to a group of dyestuffs, all built on a certain pattern, and represented by the acridine, oxazine, thiazine, selenazine and pyronine dyes, although no resistance was shown to dyestuffs of the trypan-blue type or of the triphenylmethane type.⁶ The atoxyl-resistant strains were almost unstained by oxazine dyes whereas normal strains were rapidly stained vitally and then died shortly afterwards. Another visible manifestation of the continuous effect of these dyes on trypanosomes was the production of forms devoid of the kinetoplast. The kinetoplast is not, however, lost during the process of production of atoxyl-resistant forms, and such resistant strains do not, on further treatment with acriflavine, lose the kinetoplast.⁷

A step forward in the controlled investigation of drug-resistance was the introduction by Yorke and Murgatroyd⁸ of a method for keeping trypanosomes alive at 37° for 24 hours or more *in vivo*. Using this technique, they found that an atoxyl-resistant strain was resistant *in vitro* to many substituted arsenicals, but not to sodium arsenite, and the natural conclusion was drawn that the resistance was not an arsenic-resistance, but rather a resistance to the substituted phenyl group.⁹ These *in vitro* results were confirmed by Yorke, Murgatroyd and Hawking¹⁰ by experiments in the living animal. A curious exception was found in phenylglycinearsonic acid (the pentavalent arsenical corresponding to the exceptional arsenophenylglycine of Ehrlich) in that atoxyl-resistant strains in mice showed no greater resistance to this compound than did normal strains, whereas with other arsonic acids, such as atoxyl, tryparsamide or arsacetin, there was a great difference. Yorke, Murgatroyd and Hawking¹¹ also demonstrated that strains made fast to atoxyl, arsacetin, tryparsamide, neoarsphenamine or acriflavine were identical.

The nature of the precise constitutional or physiological change which takes place in a drug-fast trypanosome is still unknown. Ehrlich, in explanation of drug-fastness, postulated a diminished affinity of certain chemoreceptors in the parasite for the drug, the non-staining of atoxyl-resistant forms by oxazine dyes being a visible demonstration of this reduced affinity. Yorke, Murgatroyd and Hawking¹⁰ were the first to show in the case of arsenicals that normal trypanosomes removed the reduced tryparsamide from the medium, as shown by a diminished direct trypanocidal action of the circumambient fluid on fresh trypanosomes, whereas drug-fast trypanosomes failed to do so. This was corroborated by Hawking¹² by chemical estimation of the arsenic content of the circumambient fluid and of the trypanosomes. It is again significant that arsenophenylglycine was absorbed by resistant and by normal strains; in addition Hawking made the interesting observation that phenylarsenoxide was also absorbed equally well by normal and resistant trypanosomes, and thus was exceptional among arsenicals of this type.

In 1930 Gough and King¹³ showed that a series of aromatic arsonic acids containing acidic groups such as carboxyl or sulpho



had no curative action on experimental trypanosomiasis in mice, but that when they were converted into amides ($AsO_3H_2 \cdot Ph \cdot CONH_2$ and $AsO_3H_2 \cdot Ph \cdot SO_3NH_2$) trypanocidal activity appeared in all cases. These

⁶ Morgenroth, *Ehrlich's Festschrift*, 1914, 572.

⁷ Leupold, *Z. Hyg. Infektionskr.*, 1925, 104, 641.

⁸ Yorke and Murgatroyd, *Ann. Trop. Med. Parasit.*, 1930, 24, 449.

⁹ Yorke, *Brit. Med. J.*, 1932, 2, 668.

¹⁰ Yorke, Murgatroyd and Hawking, *Ann. Trop. Med. Parasit.*, 1931, 25, 313.

¹¹ Yorke, Murgatroyd and Hawking, *ibid.*, 1932, 26, 577.

¹² Hawking, *J. Pharm. Exp. Ther.*, 1937, 59, 123.

¹³ Gough and King, *J. Chem. Soc.*, 1930, 669.

observations were extended by Cohen, King and Strangeways,¹⁴ who found that when the arsenical portion of the molecule was present as the arseno-grouping ($-As : As-$) then trypanocidal activity was found in five out of seven compounds, although they contained carboxyl groups. Among the active substances was arsenophenylglycine ($CO_2H \cdot CH_2 \cdot NH \cdot Ph \cdot AsO_2$), which played a salient part in Ehrlich's work on types of drug-resistance.

Having available a number of arsenoxides containing carboxyl groups, Miss Strangeways and I thought that it would be of interest to find out whether such arsenoxides act *in vitro* on atoxyl-resistant trypanosomes, and thus belong to the class represented by arsenophenylglycine, or whether they are without action and simulate the atoxyl class.

By employing the method developed by Yorke and Murgatroyd for keeping trypanosomes alive, it was found without exception that phenyl-arsenoxides containing carboxyl groups had the same lethal effect on normal and tryparsamide-resistant strains of *Trypanosoma rhodesiense*. The trypanocidal activity as shown in Table I was of a relatively low order.

TABLE I.

Compound.	Dilutions in Millions Lethal in 6 Hours.	
	Normal Strain.	Resistant Strain.
4-Carboxyphenylarsenoxide . . .	{ 0·4 0·8 0·8	{ 0·8 0·8 0·8
3-Acetamido-4-carboxyphenylarsenoxide .	0·1	0·2
4-Phenylglycinearsenoxide . . .	0·8	0·8
2 : 4-Dicarboxyphenylarsenoxide . . .	{ 0·1 0·1	{ 0·1 0·05
4-Acetamido-3-carboxyphenylarsenoxide .	0·032	0·032

We had made these, at first sight, surprising observations when Dr. Hawking told us of his finding that phenylarsenoxide acts equally well on normal and resistant trypanosomes. We were therefore encouraged to extend our experiments to a number of other arsenoxides which we had available. The results are shown in Table II.

From a close perusal of the results in these two tables, we believe that normal trypanosomes can be acted upon by arsenicals in three different ways at least. Moreover, each of these ways is but preliminary to the final chemical action which results in the death of the trypanosome. The compounds shown in Table I all contain carboxyl groups which form neutral sodium salts. These sodium salts are readily water-soluble, and are for the most part present as ions and loth to leave the watery medium. In our opinion, they can only enter the trypanosome in the same way as substances which are very soluble in water, such as glucose and salts. This also is probably the explanation for their relatively low toxicity to the trypanosome.

4-Phenylglycinearsenoxide, $CO_2H \cdot CH_2 \cdot NH \cdot Ph \cdot AsO_2$, with its acetic acid radicle, falls into this group. This oxide corresponds to arsenophenylglycine which was so important in Ehrlich's theories of types or degrees of drug-resistance and to account for which he postulated acticoceptors in the trypanosome. This oxide also corresponds to phenylglycinearsonic acid, an acid which Yorke, Murgatroyd and Hawking¹⁵ found to be

¹⁴ Cohen, King and Strangeways, *ibid.*, 1931, 3236.

TABLE II.

Compound.	Dilutions in Millions Lethal in 6 Hours.		
	Normal Strain.	Resistant Strain.	N/R Ratio.
Phenylarsenoxide. PhAsO . . .	320	640	0.5
Diglutathionylphenylthioarsinite. Ph . As< SG SG	80	80	1
p-Xylylarsenoxide. Me ₂ . Ph . AsO . .	{ 205 160	{ 205 320	0.5-1
p-Methoxyphenylarsenoxide. MeO . Ph . AsO . .	{ 205 80	{ 205 160	0.5-1
p-Thiomethylphenylarsenoxide. MeS . Ph . AsO . .	{ 320 320	{ 320 320	1
p-Acetophenonearsenoxide. CH ₃ . CO . Ph . AsO . .	{ 205 410	{ 102.5 205	2
p-Dimethylanilinoarsenoxide. NMe ₂ . Ph . AsO . .	{ 256 25.5	{ 128 52	2
p-Nitrophenylarsenoxide. NO ₂ . Ph . AsO . .	{ 2 64	{ 2 128	0.5-1
3-Nitro-4-hydroxyphenylarsenoxide. (OH)(NO ₂) . Ph . AsO . .	{ 8 26	{ 4 6.4	2-4
p-Aminophenylarsenoxide. NH ₂ . Ph . AsO . .	{ 4 8	{ 1 1	4-8
p-Methylsulphophenylarsenoxide. MeSO ₂ . Ph . AsO . .	{ 25.6 32	{ 1.6 4	8-16
p-Hydroxyphenylarsenoxide. OH . Ph . AsO . .	{ 51.2 160	{ 3.2 10	16
Diglutathionyl-p-hydroxyphenylthioarsinite. OH . Ph . As< SG SG	{ 25.6 40	{ 0.8 1.25	32
Phenyl-p,p'-diarsenoxide. AsO . Ph . AsO . .	32	1	32
p-Acetanilidearsenoxide. NHAc . Ph . AsO . .	51.2	1.6	32
Diglutathionyltryptoparsamidethioarsenite. CONH ₂ . CH ₂ . NH . Ph . As< SG . .	12.8	0.4	32
Diglutathionyl-2-hydroxy-4-acetamido- phenylthioarsinite. (NHAc)(OH)Ph . As< SG . .	{ 12.8 25.6	{ 0.2 0.8	32-64
Dicysteinylbenzamide-p-thioarsinite. CONH ₂ . Ph . As< SC SC	{ 25.6 51.2	{ 0.8 0.6	32
Benzamide-p-arsenoxide. CONH ₂ . Ph . AsO . .	{ 51.2 51.2	{ 0.8 0.8	64

anomalous. The fact that this oxide with free carboxyl group falls among these other oxides all with free carboxyl groups suggest that the critical factor in the behaviour of these phenylglycine derivatives is the carboxyl group and that postulation of aceticceptors is redundant. The observed phenomena are more readily interpreted on the basis of formation of water-soluble salts through the carboxyl groups and the distribution of this group of drugs containing carboxyl groups through the water phase as ions.

The distribution of the substances in Table II in or on the trypanosome is quite different from that of the ionised substances, and they act in at least two other ways. At one end of the table such substances as phenyl-arsenoxide and xylylarsenoxide are very active in high dilutions *in vitro*

on trypanosomes, on both normal and resistant strains alike. In chemical structure, apart from the arsenoxide group, they are devoid of markedly polar or hydrophilic groups. A few years ago Kligler and Olitzki¹⁵ showed that in *Trypanosoma evansi* 60 % of the trypanosome was lipoidal in nature. We therefore venture to suggest that phenyl- and xylyl-arsenoxides are taken up at a lipoidal-water interface in such a way that the phenyl or xylyl group is in the lipoid and the arsenoxide group is at the water interface. By such a mechanism they seem to be transported in a very facile manner, since their action is so very pronounced, to a site where the arsenoxide can exert its lethal chemical action. Since these substances act equally well on normal and resistant strains, they must act in a different way and be differently distributed from the seven substances, for example, at the bottom of the second table. These latter substances belong to the group of arsenicals in which drug-fastness was first found by Ehrlich, and they act on resistant strains only at concentrations which are between 32 and 64 times stronger than those which still act on the normal forms. These arsenoxides we suppose must be taken up by the surface or some structure in the normal trypanosome in the same way as the group of dyes represented by the acridines or oxazines. They are, in fact, substantive for the same type of structure. Of what this structure is composed in the trypanosome we know very little except that it is presumably of polar nature and not capable of adsorbing dyes of the congo-red or tri-phenylmethane types. We picture this group of arsenicals as being way-laid by adsorption on polar surfaces in normal trypanosomes *en route* to their site of action, since the concentration at which benzamidearsenoxide acts, at one extreme of the table, is so much greater than that at which phenylarsenoxide acts at the other end of the table.

Does the arsenoxide group take part in the primary fixation or are the other substituents solely responsible? To try and decide this question, phenyl-*p,p'*-diarsenoxide was synthesised, and when tested on normal and resistant strains, was found to belong to the atoxyl group of arsenicals, the N/R ratio being 32. This observation leads support to the view that in the primary fixation of this type of aromatic arsenical, both ends of the molecule are involved, and the molecule as a whole lies flat on the adsorbing surface.

In conclusion, it is tempting to try and complete the picture of the mode of action of arsenicals. The three types of distribution of aromatic arsenoxides in or on the trypanosome discussed above are merely the primary phase in the action. The final mechanism is a chemical one in which the highly reactive arsenoxide group—the toxophoric group—combines with some essential cell constituent on which the life of the trypanosome depends. With a complete knowledge of the structure and of all the reactions going on in the trypanosome-cell and of the enzymes involved, it should be possible to be certain of the final mechanism of action of an arsenical, but this state of knowledge is impossible to attain without the aid of Maxwell's sorting demons. Arsenoxides possess an intense affinity for SH groups and a water-insoluble arsenoxide dissolves readily when dusted on to the surface of a solution of glutathione. It was shown by Lohmann¹⁶ that glutathione is a specific co-enzyme for glyoxalase, an enzyme of wide distribution. If, therefore, the life of a trypanosome is dependent on glyoxalase, then this enzyme cannot function in presence of arsenoxide and the trypanosome must perish. Alternatively, there are other more important enzymes containing SH in their protein structure whose activity is dependent on the maintenance of SH in the reduced form,¹⁷ a condition incompatible with the presence of arsenoxides.

¹⁵ Kligler and Olitzki, *Ann. Trop. Med. Parasit.*, 1936, 30, 287.

¹⁶ Lohmann, *Biochem. Z.*, 1932, 254, 332.

¹⁷ Barron and Singer *Science*, 1943, 97, 356; Hellerman, *Cold Spring Harbor Symp.*, 1939, 7, 165; Bernheim and Bernheim, *ibid.*, 174; Hellerman, Chinard and Deitz, *J. Biol. Chem.*, 1943, 147, 443.

GENERAL DISCUSSION

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Dr. E. M. Lourie (*Liverpool*) said : Dr. King has drawn attention to Ehrlich's finding that trypanosomes made resistant to atoxyl and certain other arsenicals, as a result of treatment by subcurative doses of those drugs, become resistant also to non-arsenical acridine compounds. Ehrlich showed also that, conversely, trypanosomes treated by acridines are liable to acquire, coincidentally, a resistance to arsenicals. This phenomenon introduces a present-day bogey which it is necessary to enquire into, and which arises in the following way.

Mepacrine is being increasingly used for malaria in the place of quinine. Now, mepacrine is an acridine compound, and the question therefore arises whether the unrestricted use of this drug in the sleeping-sickness areas of Africa will not result in the production of strains of trypanosomes resistant to arsenicals. This would be a serious matter, since arsenical compounds are, at present, the only known effective remedies for the late stages of sleeping-sickness. Dr. Collier and I have, however, investigated the matter experimentally, and we find that very intensive treatment of trypanosomes by mepacrine, both *in vivo* and *in vitro*, does not produce a strain of parasite resistant to arsenical compounds. We conclude, therefore, that the danger of giving rise to such strains in Africa, by the increased use of mepacrine, may be dismissed as negligible.

Dr. M. A. Phillips (*London*) asked whether anything was known of the relationship, if any, of ease of de-arsenication to trypanocidal action. From the chemical point of view, de-arsenication was particularly evident in compounds containing an hydroxy group *ortho* to the arsenic atom.

Dr. King replied that he knew of no evidence in support.

Dr. H. Hurst (*Cambridge*) (*communicated*) : The experimental evidence provided by Dr. King lends further support to the theory that the cell membrane may be regarded as a visco-elastic lipo-protein mosaic structure in which primary drug fixation regulates the accessibility of the drugs to the relatively internal enzyme substrate. The work of Kligler and Oltzki indicates that the cell membrane of the parasite is relatively rich in lipid material. That this lipid material does not constitute a continuous layer or layers parallel to the cell surface is shown by the fact that drug activity cannot be correlated with the simple energy requirements of differential solubility or adsorption. The activity of phenylarsenoxide is reduced by the introduction of two oil-solubilising methylene groups into the molecule to form *p*-xylylarsenoxide, a change in molecular structure which also involves an increase in the free energy of adsorption of the molecule at an oil/water interface.

The fall in activity produced by the introduction of an additional arsenoxide group into the phenylarsenoxide molecule suggests that the enzyme substrate at which the ultimate toxic drug interaction takes place is not directly accessible to the external drug phase, since if this were the case, the availability of the arsenoxide toxophoric group would be increased by the change in the drug molecule.

The above evidence suggests that drug access is influenced both by the hydrophobic and hydrophilic portions of the molecule. The nature of the interaction of the drug molecules with the components of the cell wall may be deduced from the following considerations :

The velocity of spreading of capillary active substances at an air/water interface is very high, and may be of the order of 20 cm. per second. The driving force which influences this high rate of spreading is due to the high two-dimensional concentration gradient along the interface ; three-dimensional diffusion in the underlying bulk water phase is of a very low order, since there is no selective concentration of the capillary active molecules in the bulk phase. At an oil/water interface, two-dimensional

diffusion may be modified by the interaction of the orientated hydrophobic portion or portions of the molecules with the adjacent oil phase. In this system selectivity factors may be introduced by changes in the gross physical properties of the bulk oil and water phases, such as alteration in viscosity, or by the presence of fixed structural receptor groups which may "anchor" the capillary active molecules at the interface.

If the molecule of phenylarsenoxide is selected as a "standard," certain general conclusions may be deduced from the data summarised in Tables I and II.

(1) Trypanocidal activity is at a maximum in capillary active drugs in which the molecule contains a single arsenoxide polar group (phenylarsenoxide; *p*-xylylarsenoxide).

(2) The introduction of additional single polar groups into the "standard" molecule results in a loss in activity (phenyl-*p,p'*-diarsenoxide; *p*-hydroxyphenylarsenoxide; *p*-nitrophenylarsenoxide; *p*-aminophenylarsenide).

(3) With further increase in the number of polar groups, there is a corresponding fall in drug activity (2:4-dicarboxyphenylarsenoxide; 4-carboxyphenylarsenoxide; 4-acetamido-3-carboxyphenylarsenoxide).

The pronounced activity of dilute aqueous solutions of phenylarsenoxide and *p*-xylylarsenoxide suggests that primary drug fixation involves selective adsorption of the drug molecules at lipo-protein interfaces in the bounding cell wall of the parasite. Rapid access to the internal enzyme substrate can only be achieved when those interfaces constitute a series of channels or pathways which communicate more or less directly with the internal biophase. The drug concentration gradient across the cell wall will consist of a series of localised two-dimensional concentration gradients of high magnitude, and drug mobility will be influenced by polar and non-polar interaction of the reactants in the system. The magnitude of the changes in activity which occur when additional polar groups are introduced into the drug molecule may be attributed partly to the decrease in capillary activity, and partly to a relatively non-specific multipolar interaction between the polar portions of the drug molecules and the visco-elastic protein components at the Gibbs' layer. These factors account for the feeble trypanocidal activity of compounds such as 4-carboxyphenylarsenoxide, where the presence of water-solubilising groups will minimise adsorption at the Gibbs' layer. Drug access will mainly involve a slow three-dimensional diffusion across the bulk protein channels in the cell membrane framework, and activity will depend on the presence of relatively high drug concentrations in the bulk external drug phase.

A complicating factor in the correlation of molecular structure with trypanocidal activity is introduced by the possibility that the functional susceptibility of the parasite is influenced by the carrier activity of the drugs at the site of primary drug fixation. Further evidence in support of this might be provided from experiments on mixed drug systems.

It is interesting to note that the insecticidal activity of ethyl alcohol or phenol falls with the introduction of additional hydroxyl groups into the drug molecules; ethylene glycol and resorcinol are only feebly active. Analogous results have been obtained for drug haemolytic activity on mammalian erythrocytes.¹⁸

¹⁸ Jacobs, Glassman and Parpart, *J. Cell. Comp. Physiol.*, 1935, 7, 197.

PRINCIPLES OF INSECTICIDAL ACTION AS A GUIDE TO DRUG REACTIVITY-PHASE DISTRIBUTION RELATIONSHIPS.

BY H. HURST.

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Considerable experimental evidence¹ has accumulated which shows that the biological activity of a drug may depend on molecular interaction with the biological system involving (i) differential solubility in the cell lipoids² (Overton-Meyer), (ii) adsorption at cell interfaces³ (Traube), or more specifically (iii) polar interaction, van der Waals' non-polar interaction, and specific stereochemical relationships of the reactants in the system.⁴

The majority of the pharmacological systems which have been used in quantitative measurements of drug action are of the type in which an aqueous carrier medium serves to bring the drugs into contact with the biological system. Drug reactivity is then measured by the determination of the molar concentration of the drug which results in the production of a specific response in the biological system. It has generally been assumed that the main function of a carrier medium is to bring the drug into contact with the biological system. It has also been assumed that, where drug access to the site of action is limited by a diffusion process through an intermediary biophase or membrane, the rate of drug access is proportional to the difference between drug concentration in the external carrier medium or "source," and in the site of action or "sink." This application of Fick's Law to quantitative interpretations of drug reactivity has formed a basis which is fundamental to all permeability studies.

In the present paper the validity of these fundamental assumptions will be considered in the light of experimental evidence which has resulted during the course of a recent investigation on the mode of insecticidal action.

Drug Concentration-Biological Activity Relationships.

When immersed in pure kerosene or ethyl alcohol, mature *Calliphora erythrocephala* blowfly larvae show no marked symptoms of paralysis even after an hour or longer. Mixtures of ethyl alcohol and kerosene are extremely toxic, and the insects are immobilised within a few seconds. The permeability of the cuticle is so high in the presence of kerosene that rapid access of alcohol into the internal body fluids of the insect results in an

¹ (a) Fühner, *Arch. exp. Path. Pharmak.*, 1904, 51, 1, and 1904, 52, 69. (b) *Biochem. Z.*, 1921, 115, 235. (c) Warburg, *Biochem. Z.*, 1921, 119, 134. (d) Winterstein, *Die Narkose*, 2nd ed., Berlin, 1926. (e) Tilley and Schaffer, *J. Bact.*, 1926, 12, 303. (f) Clark, *The Mode of Action of Drugs on Cells*, 1933, London. (g) Clark, *Trans. Faraday Soc.*, 1937, 1957 (General Discussion on the Properties and Functions of Membranes, Natural and Artificial). (h) Meyer, *ibid.*, 1962. (i) Meyer and Hemmi, *Biochem. Z.*, 1935, 277, 39. (j) Ferguson, *Proc. Roy. Soc., B*, 1939, 127, 387. (k) Davson and Danielli, *The Permeability of Natural Membranes*, 1943, Cambridge.

² (a) Overton, *Jahr. Wiss. Bot.*, 1900, 34, 669; (b) *Studien über Narkose*, 1901, Jena.

³ (a) Traube, *Pflügers Arch.*, 1904, 105, 541; (b) *ibid.*, 1908, 123, 419; (c) *Verhandl. deutsch. Physik. Ges.*, 1909, 10, 800.

⁴ (a) Schulman and Rideal, *Proc. Roy. Soc., B*, 1937, 122, 29. (b) Schulman and Stenhammar, *ibid.*, 1938, 126, 356. (c) Schulman and Rideal, *Nature*, 1939, 144, 100.

increase in volume of about 50 % within three minutes. This stage is followed by the bursting of the insect when the internal pressure developed becomes excessive. These effects are produced with great rapidity by drug mixtures containing 20 to 80 % alcohol. On either side of this range equitoxic effects may be produced, showing that drug concentration in the carrier medium is not necessarily a limiting factor in biological activity when an external insecticidal mixture is brought into contact with an insect. Where the concentration of alcohol is low, biological activity increases with increase in drug concentration. But where the concentration of ethyl alcohol is high, toxicity decreases with increase in drug concentration, since within this range cuticle permeability decreases to a minimum as drug concentration increases to a maximum.

The relatively enormous increase in cuticle permeability which is induced by kerosene illustrates the influence of a diffusion factor in drug access. The importance of carrier activity is shown by the fact that ethyl alcohol-water mixtures are relatively non-toxic for all dilution ranges.

Similar effects of "induced drug access" by fat solvents such as kerosene are shown by other primary alcohols, fatty acids, ketones, amines, and phenols.⁵ In these systems, the biological activities of given drug concentrations in kerosene are logarithmically greater than the corresponding biological activities in aqueous carrier media. From this evidence, the following conclusions may be drawn:

- (1) All components of a drug mixture may contribute towards gross biological activity.
- (2) The carrier in a drug mixture may participate functionally in the biological system so as to modify the "functional susceptibility" of the biological system.
- (3) Fick's Law is invalid as a general basis for drug concentration-biological activity relationships. Drug access may increase, remain constant, or decrease with increase in drug concentration, according to the associated changes in carrier activity.

Drug-Biological System Phase Distribution Relationships.

An insight into the nature of the association of drugs with the intermediary biophases in a biological system which link the site of drug application with the site of drug action is provided from an examination of the insecticidal action of members of the homologous series of primary alcohols and fatty acids.⁶ In these series of drugs corresponding homologues differ only in the polar portions of the molecules.

The simplest method of external drug application consists in immersing the test insects in relatively large proportions of pure drug. Since the external drug phase is large in relation to the biological system, the disturbing influences of drug depletion in the external phase, and drug distribution between the carrier medium and the insect, involving possible solubility or adsorption factors, are avoided. In the homologous series of normal primary alcohols and fatty acids, the relative molar concentrations of the pure drugs decrease with increase in chain length owing to an increase in molecular volume. The total decrease in the molar concentration in each series is roughly fourfold, ascending the series from C₁ to C₈. The absolute molar concentrations of corresponding members in both series are approximately equal.

The bulk internal biophase of an insect is essentially aqueous. When a solution of a drug in a non-aqueous carrier is injected into the haemolymph, complications which might arise owing to the possible influence on biological activity of drug distribution between the mutually immiscible haemolymph/carrier phases may be avoided by the injection of aqueous drug solutions.

⁵ Hurst, *Nature*, 1940, 145, 462.

⁶ *Ibid.*, 1943, 152, 292.

The relative external and internal biological activities of members of the homologous series of normal primary alcohols and fatty acids are shown in the graphs (Fig. 1 (a), (b)). Each point on the curves represents the average of 10 determinations of biological activity on insects selected from a uniform batch (mature *Phormia terraenovae* blowfly larvae). The drugs were administered externally by immersing the test insects in 10 c.c. samples of each member of the drug series. Biological activity was measured on a time-action basis when the drugs were applied externally. Survival time gave the most clearly defined criterion of activity under these conditions (Fig. 1(a)). Paralysis was selected as an index of internal biological activity when the drugs were injected directly into the haemolymph; owing to gradual leakage of drug and internal body fluids from the site of injection, death was a less reliable criterion of biological activity than paralysis. Comparison between external and internal drug reactivities may be made on the assumption that external biological activity is inversely proportional to survival time, and internal biological activity inversely proportional to the isoactive molar concentrations in the dosages injected, which were roughly 25 mg./100 mg. body weight. The reciprocals of the threshold molar concentrations which induce paralysis are expressed as arbitrary numerical indices of molecular activity (Fig. 1 (b)).

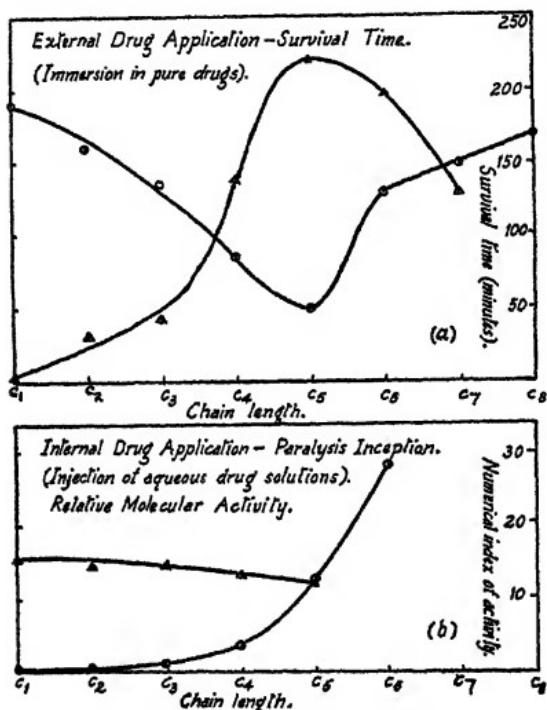


FIG. 1.—The relative external and internal biological activities of members of the homologous series of normal primary alcohols and fatty acids (Test Insect, *Phormia terraenovae*).

○ Alcohols. △ Fatty acids.

drug access cannot be correlated with simple drug-cuticle phase distribution relationships. Within the range C₁ to C₈ the penetration of the alcohols increases with chain length and reaches a maximum at C₅. Within a corresponding range, there is a relatively enormous decrease in the rate of penetration of the fatty acids; drug access is at a minimum at a chain length of C₅. This divergence in drug access as both series of drugs are ascended from C₁ to C₅ changes to a convergence as the series are ascended further from C₅ to C₇. At C₇, survival times are of a similar order in both series. (C₈ in the fatty acid series is solid at normal room temperatures, and is therefore unsuitable for comparison with the corresponding liquid alcohol homologue.)

Analysis of the data summarised in the graphs shows that

Difficulties arise when an attempt is made to correlate the relative external biological activities of the drugs with the internal biological activities. For systems in which the drugs are applied internally, there is a rough proportionality in the alcohol series between molecular activity and chain length within the restricted range C_1 to C_5 . In the fatty acid series, internal application shows that the *isoactive molar concentrations remain relatively constant* as the series is ascended from C_1 to C_5 . Increase in chain length produces no increase in biological activity which is comparable with the exponential rate of change shown by the alcohols within this range. Where the chain length is short (C_1) the molecular activity of the fatty acids (formic acid) is roughly about 80 times that of the alcohol homologue (methyl alcohol). The dominant influence of chain length in both series is shown at C_5 when valeric acid is isoactive with amyl alcohol. In both series the *intensity* of narcosis produced by internal drug application decreases as the chain length exceeds C_5 . This change is most pronounced in the fatty acid series, and saturated aqueous drug solutions produce only incomplete paralysis.

From this evidence the following conclusions may be drawn :

(1) Where diffusion through an intermediary biophase which links the site of drug application with the site of drug interaction in the biological system is a limiting factor in drug access, relative biological activity measured at the site of drug application may differ from relative drug activity at the ultimate site of action. Drug reactivity may increase, remain relatively constant, or decrease as a homologous series of drugs is ascended, according to the mode and the site of application.

(2) Quantitative measurements of drug reactivity have generally been based on comparison of the molar concentrations which produce equi-toxic or equi-narcotic effects on selected biological test systems. The mode of application of a drug is generally severely restricted by the biological component of the pharmacological system. For example, systems such as erythrocytes, protozoa, bacteria, or isolated preparations of heart, muscle, nerve, and other tissues are usually examined when in contact with physiological media of which water is a major component. The ranges of drugs and drug concentrations are limited by physico-chemical factors, such as solubility, and the aqueous carrier medium must be carefully selected to maintain a condition of physiological balance with the biological system during the period of experimental observation. In systems of this type, correlation of drug reactivity with solubility in the cell lipoids (Overton-Meyer) or with adsorption at cell interfaces (Traube) may lead to ambiguity, since in homologous series, physical properties such as differential oil/water solubility, capillary activity, viscosity, or vapour pressure *change uniformly in the same direction* as the series are ascended. An exponential relation between molecular drug activity and length of hydrocarbon chain may simply express the tendency of the hydrocarbon portions of the drug molecules to escape from the aqueous carrier medium into the lipid centres of the biological system. Since these lipoids are invariably associated with other relatively hydrophilic substances (e.g. proteins) to form complex systems of interfaces, it is difficult to exclude the possibility of adsorption as a factor in drug-biological system phase distribution relationships where the drugs are capillary active.

This complicating influence of phase distribution between a carrier medium and the biological component of a pharmacological system disappears when the biological system is brought into contact with pure drugs. Biological activity is now chiefly influenced by molecular interaction in the actual biophases of the biological system. By the use of relatively resistant test organisms, such as blowfly larvae, the influence of both polar and non-polar portions of the drug molecules is shown clearly by the gross divergence between the relative biological activities of the alcohols and fatty acids when corresponding homologues are compared. The

results recorded in Fig. 1 show that drug reactivity cannot be attributed solely to simple distribution between immiscible phases based on differential solubility or adsorption factors.

Mechanism of Drug Access.

The experimental evidence which has been provided shows that the measurement of the biological activity of a drug involves a precise definition of the nature and site of drug interaction. When drugs are applied externally to insects, the primary site of drug interaction, irrespective of biological response, is at the external surface of the cuticle. Secondary interactions may occur at specific receptors or loci in the intermediary chain of biophases (i) bulk cuticle framework, (ii) haemolymph and associated tissues.

Nature of Cuticle Surface.—When blowfly larvae are suspended at an air/water interface, a monomolecular film spreads outwards along the interface. This surface film gels reversible at low surface pressures (2-4 dynes/cm.), and becomes coherent and rigid when tannic acid is injected into the underlying water phase. This indicates the presence of proteins at the cuticle surface, since similar effects are shown with long chain amine or protein monolayers. The "tanning" of these films is due to the multiple-point interaction of the polar groups in the tannic acid molecule with the ionised amine groups in the surface film.¹³

The presence of lipoid components at the cuticle surface is shown by the narcotic action of fat solvents. Blowfly larvae become rapidly paralysed when immersed in the lower members (C_6 to C_8) of the homologous series of paraffins. Narcosis occurs within 1 to 2 minutes, even when the entrance of the drugs into the tracheæ is precluded by blockage of the spiracles. Since paraffins are insoluble in proteins, drug access must take place through lipoid loci at the cuticle surface. From this evidence it may be concluded that the surface of the cuticle in blowfly larvae is not homogeneous but composite, and consists of heterogeneous protein and lipoid associations or "patches" suggestive of a mosaic ultrastructure.

Bulk Cuticle Framework.—There are two primary layers in a typical insect cuticle, an outer "lipoid" layer, or epicuticle, and an inner chitin-protein layer.⁷ The epicuticle is secreted as a thin hydrophilic membrane by the epidermal cells. It is later "tanned" and impregnated with lipoid material, which by a process of condensation and polymerisation becomes relatively resistant to the disruptive action of fat solvents and strong mineral acids.⁸ The inner layer of the cuticle consists of a chitin framework which is closely associated with the protein components. These are relatively water-soluble in blowfly larvae.⁹ The bulk cuticle phase is permeated by a fatty secretion of the epidermal cells. This secretion passes through the cuticle along specialised ducts to the outer epicuticle; there is probably a more general transmission of lipoid secretion through the "pore canals" which form a network in the inner chitin-protein layer but do not pass through the epicuticle framework.

It is clear from this brief description of the gross morphology that the cuticle consists of a complex system of heterogeneous phases, and correlation of biological activity of drug systems present as an external phase with cuticle permeability involves a specific definition of the limiting factors in drug-cuticle interaction.

Action of Fat Solvents.—Early in the present account it was shown that fat solvents such as kerosene exert a marked synergistic action on

⁷ Kühnelt, *Zool. Jahrb. Abt. Anat.*, 1928, 50, 219.

⁸ (a) Wigglesworth, *Quart. J. Micr. Sci.*, 1933, 76, 270; (b) *The Principles of Insect Physiology*, 1939, London.

⁹ (a) Fraenkel and Rudall, *ibid.*, 129, 1. (b) Trim, *Biochem. J.*, 1941, 35, 1088.

the rate of transmission of ethyl alcohol through the cuticle of blowfly larvae. Not only does the insect swell owing to rapid diffusion of the alcohol into the internal body fluids, but a cloudy swirling zone appears immediately outside the cuticle owing to the displacement of kerosene from the drug mixture by water which diffuses outwards from the cuticle.⁵ Similar effects have been described for other insects. Water also passes outwards from the cuticle when the insects are immersed in oils alone; owing to insolubility in the oil phase, the water assumes the form of minute droplets attached to the surface of the cuticle.¹⁰

Induced access of drugs owing to carrier activity does not depend primarily on vital transport through the bulk cuticle framework; fat solvents such as kerosene induce drug access through the cuticles of dead blowfly larvae. Analogous effects have also been obtained in synthetic systems in which a drug phase is separated from an aqueous phase by an isolated cuticle "membrane," or by a discrete component layer of the cuticle. The permeability of all component layers of the cuticle is increased by kerosene. The degree of induced drug penetration is most marked through the extreme outer layer, or epicuticle,⁶ in which the preponderance of lipid constituents has been demonstrated histologically.

The association of fat solvents with the cuticle framework is primarily physical, and the changes in permeability which are induced are readily reversible. For example, *Calliphora* larvae will swell rapidly in ethyl alcohol-kerosene mixtures, but further access of alcohol ceases when the insects are transferred to pure ethyl alcohol owing to "wash-out" of kerosene from the cuticle framework. Similar effects are shown with isolated cuticle preparations. This shows clearly the reversible nature of the functional changes in cuticle permeability which are induced by the association of the carrier in a drug mixture with the cuticle framework.

After prolonged immersion in fat solvents, an irreversible increase in cuticle permeability takes place. This is shown by (i) an increase in the original rate of water loss by evaporation through the cuticle, and (ii) by a marked increase in the rate of access of pure drugs such as methyl or ethyl alcohol. After this treatment, the rate of drug access is still further increased by oil carriers such as kerosene, showing that only a proportion of the lipid components are dispersed or removed by fat solvent action. This provides striking evidence that drug access does not depend primarily on solubility in the lipoids, since removal of lipoids from the cuticle would hardly facilitate drug access if this were the case. The main site of carrier activity is in the outer layers of the outer layer of the cuticle. When the epicuticle is removed or mechanically damaged, the insect loses its capacity for the conservation of water and rapidly becomes desiccated, showing that the inner chitin-protein layer is relatively permeable to water. When the epicuticle is removed carrier activity in the residual cuticle layers is relatively slight.

The physical nature of the oil carrier has a marked influence on carrier activity. In the series hexane → octane → decane → dodecane (kerosene range) → heavy oil (medicinal paraffin range) carrier activity decreases with increase in viscosity of the carrier. These factors are relatively independent of carrier toxicity. For example, narcotic activity of the homologous series of paraffins to blowfly larvae shows a sharp "cut-off" as the series is ascended in the range $C_8 \rightarrow C_{10}$; dodecane (C_{12}) is relatively non-toxic. Within the range $C_8 \rightarrow C_{12}$ carrier activity is very pronounced, but the penetration of ethyl alcohol through the cuticle is only moderately increased by relatively viscous oils such as "thick Nujol," or medicinal paraffin.

¹⁰ Wigglesworth, *Bull. Ent. Res.*, 1942, 33, 205.

Physico-chemical Changes in Cuticle Framework produced by the Action of Fat Solvents.

From the experimental evidence which has been provided the changes in functional cuticle permeability which are produced by the association of fat solvent carriers with the cuticle framework may be attributed to :

(i) A van der Waals' interaction between the fat solvent molecules and the lipoids of the cuticle, involving a reduction in mutual cohesion between the lipophilic elements or chains, and resulting in the production of a relatively open three-dimensional chemically linked network which encloses the more "labile" lipid components in which the solvent molecules participate functionally. In this way the fat solvent increases the free volume of the lipid phase, and may also act as a "bridging" medium which links discrete lipophilic patches in the bulk cuticle phase. Since both protein and lipid components are enclosed in an elastic lattice framework, molecular alterations in the lipid phase will probably induce associated changes in molecular orientation in the protein phase. The decrease in carrier activity which takes place with increase in carrier viscosity suggests that the bulk lipid phase is normally of high "functional viscosity." The term "functional viscosity" is not strictly comparable with Newtonian viscosity in a homogeneous liquid, since the protein and lipid phases of the cuticle are heterogeneous visco-elastic systems comprising chemically-linked networks which enclose the more "mobile" components. "Functional viscosity" gives a measure of the "yield value" of the lipid phase to drug diffusion pressure.

(ii) A secondary irreversible increase in the flexibility of the lipophilic lattice elements owing to a rupture of the cross-linkages which normally regulate the stability and elasticity of the lipophilic chains. The elastic restoring forces of the lattice framework oppose the dispersive or disruptive action of the fat solvent. The irreversible increase in permeability, which probably involves an increase in free volume in the bulk lipid phase, is due to the removal of "labile" bonding components by fat solvent action, resulting in increased flexibility or mobility of the residual lattice chains. This would account for the increase in the mobility of water molecules especially in the outer layers or epicuticle, and also explains the increase in the permeability of the cuticle to drugs such as fat soluble alcohols when a proportion of the lipoids of the cuticle have been removed by prolonged fat solvent action.

Action of "Inert" Powders or Dusts.

Additional evidence which supports the suggestion that the labile cuticle components act as a "bonding" phase which regulates the cohesion of the chemically-linked cuticle lattice elements is provided by the insecticidal action of "inert" powders or dusts.

Finely divided powders such as quartz or charcoal readily adsorb the relatively labile lipid or lipo-protein components from the surface of the epicuticle. This process is non-specific, and depends on the adsorptive and storage capacities of the powder for the capillary active cuticle components, and also on the capacity of the epicuticle/powder interface for the transmission of these components. When the rate of removal of lipid by adsorption displacement exceeds its rate of replenishment by transmission from the epidermal cells to the epicuticle, irreversible secondary changes are produced in the epicuticle framework. This suggests that the labile components of the epicuticle constitute a bridging or bonding phase which links the flexible lipophilic elements of the epicuticle framework. Depletion of this labile "bonding" phase results in a reduction in lateral cohesion of the lattice elements, and this permits an increase in the mobility of water molecules in the bulk epicuticle phase. Once this

stage is reached, the insect is unable to control the rate of transmission of water through the cuticle, even when the external powder phase is removed, and rapid water loss soon results in death from desiccation.

In the normal insect, variation in the rate of secretion of the "bonding" phase by the epidermal cells may result in corresponding changes in free volume and functional viscosity of the bulk epicuticle lipid phase, thus providing a very sensitive regulatory mechanism for the control of water loss. "Inert" dusts also increase the rate of water loss through the cuticle of dead insects, although the "latent" period between dust application and eventual desiccation is relatively small owing to the absence of secretory activity of the epidermal cells. This is of interest, since in the living insect the regulatory action of the spiracles is a disturbing influence in the assessment of dust/cuticle water loss relationships. Analogous effects, which have been obtained in synthetic systems using artificial membranes as models of insect cuticle, have provided a very useful basis for predicting the toxicity of insecticidal dusts.

Carrier and Dispersant Action in Mixed Drug Systems.

Extending these concepts of carrier action, it is seen that a drug may either induce its own access through the cuticle or exert a carrier action in mixed drug systems which is similar to that produced by fat solvents. For example, the survival time of *Calliphora erythrocephala* larvae in ethyl alcohol-octyl alcohol mixtures is shorter than the respective survival times in the pure drug components. This test insect is more susceptible than *Phormia terraenovae* larvae. Typical data showing the change in survival time with change in the relative proportions of the components in ethyl alcohol-octyl alcohol mixtures are shown in Table I. The data

TABLE I.—BIOLOGICAL ACTIVITY OF ETHYL ALCOHOL-OCTYL ALCOHOL MIXTURES.

Drug System % Ethyl Alcohol.	Survival Time (mins.) (<i>Calliphora</i> larvae).
100	97
75	16
50	1.5
25	3
0	7.5

TABLE II.—BIOLOGICAL ACTIVITY OF AMYL ALCOHOL-CETYL ALCOHOL MIXTURES.

Drug System % Amyl Alcohol.	Survival Time (mins.) (<i>Calliphora</i> larvae).
100	5.5
99	6.5
97	9.5
95	19.5

in the table illustrate an example of *drug synergism* in which selective access of one component (ethyl alcohol) into the internal biophases of the biological system is induced by selective carrier action of another component (octyl alcohol) at a biophase, the cuticle, which is remote from the ultimate site of drug interaction. The action of octyl alcohol is similar to that of kerosene, but since the octyl alcohol itself is active, a factor of *carrier toxicity* is also involved in addition to *carrier activity*.

Comparison of carrier activities in various mixed drug systems shows that in the homologous series of alcohols, carrier activity increases to a maximum and then decreases as the series is ascended and capillary activity becomes pronounced. In fact, strongly capillary active alcohols such as cetyl alcohol exert "negative carrier activity," or *antagonism* on the rate of access of drugs of relatively low capillary activity (Table II).

It is seen from the data in the table that relatively small proportions of cetyl alcohol are effective in reducing the biological activity of the major component of the drug mixture (amyl alcohol).

In the homologous series of fatty acids, carrier activity is less marked than in the alcohol series and becomes pronounced at a later stage (C_6 to C_7) than in the alcohols (C_4 to C_5).

Drug-cuticle Phase Distribution Relationships.

The experimental evidence which has been here provided may be used as a basis for the interpretation of more specific factors in drug access. It is clear that the cuticle framework cannot be regarded as a homogeneous phase, but is more analogous to a composite visco-elastic system of liquid/liquid interfaces, comprising a hydrophilic protein gel phase which is associated with a hydrophilic lipid phase of high "functional viscosity."

Drug penetration through the bulk cuticle framework may involve:

- (1) Diffusion through the bulk protein phase.
- (2) Diffusion through the bulk lipid phase.
- (3) Free diffusion through the pores or canals in the bulk cuticle framework.
- (4) Free diffusion through a bulk cuticle phase in which the lipid and protein components are rendered mutually miscible, or functionally homogeneous by the dispersant action of the drug components.
- (5) Two-dimensional diffusion along the Gibbs' layer, or internal network of liquid/liquid interfaces.

The experimental evidence does not support drug access through the bulk protein or lipid phases. From differential solubility considerations alone, the rate of change in drug access should proceed uniformly and in the same direction in both homologous series of alcohols and fatty acids as the series are ascended. Similarly, any attempt to correlate drug penetration with adsorption at liquid interfaces of the oil/water type is precluded, since the work of adsorption of alcohols and fatty acids at an oil/water interface increases uniformly in both series as surface activity increases.

Structurally, the cuticle framework contains an extensive system of "pore canals" which extend from the inner epidermal cells to the inner surface of the epicuticle.^{8a, b, 10, 11} That molecular "sieve action" is not a limiting factor in drug access is shown by the following evidence:

- (i) The main site of induced drug access is in the outer epicuticle layer, which does not contain macroscopic pore canals.^{8b}
- (ii) Molecular volume increases in both series of alcohols and fatty acids as the series are ascended. Drug access may either increase or decrease in both series (Fig. 1 (a)).

The possibility also exists that interaction of the external drug mixture with the heterogeneous lipid and protein components of the cuticle induces mutual dispersion or "emulsification" of these components so that drug access is mainly influenced by the concentration gradient across a functionally "homogeneous" bulk cuticle phase. This possibility is precluded by the following evidence:

- (i) Concentrated aqueous solutions of protein and lipid dispersant such as sodium cetyl sulphate are relatively non-toxic to blowfly larvae, and fail to disrupt the epicuticle framework. After immersion in 25% aqueous sodium cetyl sulphate for half an hour, blowfly larvae are still active and resistant to pure methyl or ethyl alcohol.

(ii) Systems (e.g. oleic acid, oleyl alcohol, cetyl alcohol) which should induce emulsification of the lipid and protein cuticle components exert a pronounced antagonistic action when incorporated in an external drug phase such as amyl alcohol, or ethyl alcohol-kerosene mixtures (cf. Table II).

The experimental evidence favours a two-dimensional surface diffusion along the Gibbs' layer or functional interfaces of the lipo-protein mosaic.

¹¹ Dennell, *Nature*, 1943, 152, 50.

The physico-chemical factors which may influence this mode of drug access include :

- (i) Concentration at the Gibbs' layer.
- (ii) Spreading coefficient at the Gibbs' layer.
- (iii) Physical nature of the adsorbed monomolecular film.
- (iv) Functional viscosity of bulk lipid phase.
- (v) Functional viscosity of bulk protein phase.
- (vi) Presence of other capillary active reactants at the Gibbs' layer.
- (vii) Specific molecular interaction of drug molecules with functional cuticle components at the Gibbs' layer.

Under conditions in which the viscosity of the bulk lipid phase is not a limiting factor in drug access, *i.e.* with pure drugs or drug-kerosene mixtures within the range C_1 to C_8 , the biological activity of the alcohols present as an external drug phase falls rapidly as the series is ascended. This cannot be attributed to changes in *internal* molecular activity as measured by injection of the drugs into the haemolymph. Since capillary activity increases in the direction C_1 to C_8 , the relative degree of adsorption also increases in this direction. It is clear, from these considerations, that molecular drug concentration at the Gibbs' layer is not a limiting factor in drug access.

In homologous series, the spreading coefficient at the Gibbs' layer decreases as the hydrocarbon chains of the drug molecules become longer. This is due to an increase in the mutual cohesion between the molecules at the surface. Within the range C_1 to C_8 the adhesion between the hydrocarbon chains is relatively small, and the molecules from mobile "gaseous" films.¹² The adsorption of drugs at the functional liquid/liquid interfaces in the cuticle framework is primarily influenced by the work of adsorption at an oil/water interface. The rate of spreading or the mobility of an alcohol, *e.g.* octyl alcohol, at the oil/water interface may be slowed down considerably by increase in viscosity of (i) either of the bulk phases, or (ii) by the presence of an adsorbed interfacial film of moderately high capillary activity (*e.g.* cholesterol, cetyl alcohol, oleyl alcohol).

The above considerations suggest that the limiting factors which influence two-dimensional drug diffusion through the cuticle framework are :

- (i) Polar interaction of the drug molecules with the protein components at the Gibbs' layer.
- (ii) Non-polar van der Waals' interaction between the hydrocarbon chains of the drug molecules and the lipid components at the Gibbs' layer.
- (iii) Interfacial viscosity at the Gibbs' layer, which may be modified experimentally by the presence of substances of high capillary activity in the external drug phase. Selective adsorption of these substances results in a blocking of the interface, thereby producing a decrease in the accessibility to other components in the external drug mixture which are of lower surface activity.

Two-dimensional drug diffusion along the Gibbs' layer does not preclude three-dimensional diffusion through the bulk lipid and protein phases, which probably is predominant with non-capillary active systems, but from this elucidation of the limiting factors in capillary active drug access, it is now possible to explain the gross divergence in drug access between the alcohols and fatty acids recorded in Fig. 1.

Penetration of Alcohols.—Owing to weak polar interaction of alcohols with the proteins of the cuticle, and weak non-polar interaction of the lower members (C_1 to C_8) with the lipoids, carrier activity of the drugs is relatively feeble within this range. As the series is ascended from C_1 to

¹² Adam, *The Physics and Chemistry of Surfaces*, London, 1941.

C_6 , the increase in carrier activity owing to dispersant action of the alcohols on the lipid phase results in an increase in functional cuticle permeability. A specificity factor appears to be involved in the non-polar interaction of the drug molecules with the lipoids of the cuticle, for dispersant action decreases as the series is ascended further from C_6 to C_8 , within which range drug access also diminishes. It is possible, however, that with increase in chain length, the increase in the cohesion of the drug molecules becomes a limiting factor in mobility within the range C_6 to C_8 .

Penetration of Fatty Acids.—The strong polar interaction of fatty acids with the protein components of the cuticle is sufficient to induce a selective penetration through the protein phase by the preliminary rupture or

dispersion of salt interlinkage systems (*e.g.* $-\text{COO} \text{NH}_3^+$) owing to competition of the polar groups of the drug molecules. Evidence for this assumption is provided by the penetration and expansion of synthetic monomolecular amine and protein films by fatty acids.¹³ It is possible to visualise a competition between the lipid and the protein components of the cuticle for the fatty acid drug molecules. Where chain length is short (*e.g.* formic acid) polar group interaction will be a limiting factor in drug access. Rapid penetration through the cuticle takes place through the protein phase since the weak short range van der Waals' attraction forces between the drug molecules and the lipid phase are not limiting factors in drug mobility at the Gibbs' layer. As capillary activity increases, the drug molecules tend to become anchored at the external layers of the cuticle owing to a balance between the polar and non-polar interactions of the molecules with the lipo-protein associations at the Gibbs' layer. The stability of the lipo-protein-drug association reaches a maximum at C_6 (valeric acid) when drug access is at a minimum. From C_6 to C_8 , this stability decreases as the influence of non-polar interaction begins to predominate over the competing influence of polar interaction. Dispersion of the lipid phase now becomes a limiting factor in drug access, and increase in functional cuticle permeability accounts for the increase in drug reactivity within this range.

The dispersant action of drugs and fat solvent carriers on the cuticle is extremely complex. In lipo-protein associations, dispersant action must certainly involve both lipid and protein components since these are invariably closely associated in living biological systems, and related changes in molecular orientation will take place depending on the elasticity of the bounding lattice framework. It is likely that the functional liquid/liquid interfaces in the cuticle framework are saturated with the relatively labile capillary active lipo-protein associations initially secreted by the internal epidermal cells. Primarily, dispersant action may involve a reversible reduction in the mutual cohesion of the labile lipo-protein associations at the Gibbs' layer. Monolayers of sterols are readily penetrated by short chain fatty acids or alcohols resulting in the formation of mobile "gaseous" films.¹⁴ Prolonged association of the cuticle with drugs or fat solvents produces an irreversible increase in permeability, which may be correlated with displacement of the lipo-protein associations; in this condition the cuticle is in a state of physiological unbalance, which is reflected by the increase in the rate of water loss. In the normal insect conservation of essential water is a major physiological role of the cuticle framework, and this is achieved by the modification of the extreme outer layer to form the epicuticle.

Induced access of drugs by non-polar solvents such as hexane, octane, or dodecane, may be ascribed largely to a decrease in the functional viscosity of the lipid phase resulting in a large increase in functional cuticle permeability. The fact that induced penetration does not occur in an aqueous carrier medium suggests that the gel structure of the protein

¹³ Cockbain and Schulman, *Trans. Faraday Soc.*, 1939, 25, 716.

phase is relatively compact, and the possible swelling action of the carrier medium by participation in the protein phase, is insufficient to permit access of drugs even when the molecular volumes are small. Induced penetration occurs with polar carriers of moderate capillary activity (e.g. octyl alcohol) since the increase in drug mobility owing to dispersant carrier action is a more important factor in drug access than the opposing influence of carrier adsorption at the Gibbs' layer. Where the capillary activity of the carrier is high (e.g. cetyl alcohol, oleyl alcohol, cholesterol, or oleic acid), blockage of the Gibbs' layer by selective carrier adsorption accounts for the antagonistic influence of carrier activity on drug access.

Drug Reactivity at the Site of Action.

If the valid assumption be made that the primary interaction of drugs injected into the haemolymph takes place at specific lipoid or protein loci, and that the interactions at specific enzyme centres embedded in the lipo-protein associations occur secondarily, it becomes possible to correlate internal molecular drug reactivity with external drug reactivity, where diffusion to the site of action is a disturbing influence.

From Fig. 1 (b), it is seen that the relation between internal molecular activity and chain length of the homologous series of alcohols approximates to an exponential form which is characteristic of pharmacological data expressing equilibria between drugs and cells. This indicates that, where diffusion to the site of action is not a limiting factor in drug access, biological activity depends on the van der Waals' interaction of the non-polar portions of the drug molecules with the lipoid loci at the specific cell receptors.

The molecular isoactivity of the fatty acids as the series is ascended from C₁ to C₈ suggests that, within this range, biological activity is influenced chiefly by head group interaction of the polar portions of the drug molecules with the protein receptors at the site of action; increase in length of hydrocarbon chain produces no increase in biological activity which is comparable with the logarithmic rate of change shown by the alcohols. Where chain length is short, the molecular activity of the fatty acids is much higher than that of the corresponding alcohol homologues. The influence of chain length is shown by the fact that at C₈ both series are isoactive, showing that a critical value in the van der Waals' interaction of the drug molecules with the lipoid centres has been attained. When the drugs are applied externally, this critical value is also reached at a chain length of C₈, but the selective molecular interaction of the drugs with the cuticle framework, owing to selective polar interaction of the fatty acids with the protein components, results in a *maximum divergence in relative drug reactivity* (Fig. 1 (a)) showing clearly the influence of a limiting diffusion factor.

Molecular Interaction as a Factor in Narcosis.

The theory, first proposed by Overton and H. Meyer, that narcosis depends on the interaction of the drugs with the cell lipoids has recently been formulated in a more general manner by K. H. Meyer:¹²

"Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipoids of the cell (or, to be more precise, in the lipoidic alcohols of the cell substance). This concentration depends on the nature of the animal or cell, but is independent of the narcotic."

Meyer points out that this rule has nothing to do with membranes, but is merely an expression of the fact that the irritability of the cell is diminished when the lipoidic alcohols of the cell become charged with a limiting threshold concentration of narcotic. The evidence provided was based on comparison of the isoactive concentrations of gaseous and water-soluble narcotics which produce narcosis when applied as an *external*

drug phase to mice and tadpoles respectively. From the experimental evidence obtained, Meyer concludes that there is no kind of correspondence between narcotic activity and surface activity, and that any theory which is based on a connection between these two is not in agreement with the facts.

On the other hand, the regularity was observed that the concentration in oleyl alcohol as set up in equilibrium with the effective concentration in the medium (air or water) is always constant, or nearly so. Correlation of biological activity with solution in the cell lipoidic alcohols was based in this analogy of drug phase distribution relationships.

Clark and other workers have stressed the fact that the regularity with which the pharmacological activity of narcotics increases with length of hydrocarbon chain may be explained most readily by the hypothesis that the narcotics are adsorbed on surfaces in the cells, although most of the results are consistent with the alternative hypothesis that drugs dissolve in and alter the cell lipoids.^{1a, f, j, 2}

When the experimental facts of observation are in accord with either of two fundamental physico-chemical laws, i.e. (1) distribution between immiscible phases depending on differential solubility, or (2) distribution depending on adsorption at interfaces, the apparent ambiguity disappears in a wider statement of theory, or in more specific definition of the variable factors in the particular systems. The chief difficulty in the interpretation of the significance of pharmacological data has been the lack of precision in the experimental evidence as to the nature of drug-biological system phase distribution relationships. This ambiguity disappears when the nature and site of drug interaction is more clearly defined. Comparison of the biological responses produced by injections of aqueous solutions of alcohols and fatty acids into the haemolymph of *Phormia* larvae shows :

(i) The narcotic symptoms produced by injection of the lower members C_1 to C_8 in both series of drugs are relatively ill-defined. Drug tolerance is small within this range. Drug concentrations above the threshold narcotic values produce rapid pathological changes in the tissues resulting in death shortly after drug injection.

(ii) *Intensity* of narcosis and tolerance to higher concentrations than the threshold narcotic dosages reaches a maximum at C_8 .

(iii) With further increase in chain length (C_8 to C_{12}) the intensity of narcosis decreases in both series. With the alcohols, this becomes most apparent at C_{12} ; *saturated* aqueous solutions of higher homologues are relatively inactive when injected, and fail to produce complete paralysis. With the fatty acids, biological activity falls off at a slightly earlier stage (C_8); *saturated* solutions of higher members are relatively inactive.

If biological activity is measured by the *intensity* and *duration* of the symptoms of paralysis produced by drug injection, correlation between the molecular activities of the alcohols and fatty acids is shown at a chain length of C_8 . The relative differences in activity between the lower members in both series may be attributed to chemical reactivity due to head group interaction of the drug molecules with the protein receptor groups in the biological system. At C_8 , van der Waals' interaction between the hydrocarbon chains of the drug molecules and the lipid receptors becomes a limiting factor in drug reactivity in the *particular systems used*. This suggests that narcosis is influenced by specific non-polar stereochemical relationships between the drug molecules and the lipid receptors at the site of action. The marked analogy between the *nature* of the interactions of drug molecules with the lipo-protein associations of the cuticle framework and the internal receptors at the site of action suggests that adsorption at functional lipid/protein interfaces within the insect is a major factor in biological activity.

The dominant influence of a diffusion factor in measurements of drug reactivity is shown clearly by the following experimental evidence:

During the mature larval stage, the cuticle of the blowfly *Phormia terraenovae* increases greatly in thickness, and the relative resistance to drugs such as alcohols and fatty acids applied externally increases during this stage. The relative resistance to drugs applied internally by injection into the haemolymph shows no marked change as pupation approaches. Similar experiments on the related series of blowfly larvae

(a) *Calliphora erythrocephala*

(b) *Phormia terraenovae*

(c) *Sarcophaga falculata*

show that functional cuticle permeability and relative susceptibility to drugs applied externally decreases in the direction (a) → (b) → (c). When the drugs are applied internally by injection, molecular isoactivity is shown by corresponding homologues in all three species of test insect. These experiments show that the "biological activity" of a drug has little quantitative significance unless the mode of drug application and the drug-biological system phase distribution relationships are clearly defined.

When *Calliphora erythrocephala* larvae are immersed in pure alcohols, penetration through the cuticle takes place more rapidly than through the cuticle of *Phormia* larvae (Fig. 1 (a)). Since the internal molecular activities are of a similar order, it is permissible to compare the relative external activity per molecule by the reciprocals of the survival times when the insects are immersed in pure drugs, taking as unity the survival time in pure methyl alcohol for each organism. The results are recorded in Table III. The results show that with both test insects molecular activity increases from C₁ to C₆ as the series of drugs is ascended, but the rate of increase in biological activity is much more pronounced with *Calliphora* than with *Phormia*. From C₆ to C₈ biological activity falls in both systems.

TABLE III.—RELATIVE EXTERNAL BIOLOGICAL ACTIVITIES OF HOMOLOGOUS SERIES OF ALCOHOLS TO INSECTS OF DIFFERENT SUSCEPTIBILITY.

Length of Chain.	Survival Time (mins.).		Molecular Activity.	
	<i>Phormia</i> .	<i>Calliphora</i> .	<i>Phormia</i> .	<i>Calliphora</i>
C ₁	190	125	1.00	1.00
C ₂	160	93	1.18	1.34
C ₃	135	25	1.41	3.58
C ₄	85	7	2.23	17.9
C ₅	50	5.5	3.8	25.0
C ₆	125	6	1.52	20.8
C ₇	150	7.5	1.26	16.7
C ₈	170	9.5	1.12	13.2

These results have an important bearing on interpretations of drug specificity in pharmacological systems. It has generally been assumed that drug specificity depends mainly on the nature of the molecular interaction of the drug with the ultimate cell receptors in the biological system. Where differences in drug access are limiting factors in biological activity in a range of biological systems, the relative biological activities of a range of drugs measured with one particular biological test system may differ considerably from the corresponding biological activities measured with another system, even though the molecular activities at the sites of action in the systems are similar. This may be attributed to the selective action on drug access of drug molecular interaction with intermediary biophases in the biological system which link the drug "source" with the drug "sink."

Still further complexities appear when the range of biological systems is extended to include other insects. By far the majority of insects (*e.g.* adult Diptera, larval and adult stages of Coleoptera, Lepidoptera, nymphal and adult stages of Orthoptera, Hemiptera) become rapidly immobilised when immersed in pure drugs such as alcohols and fatty acids, and bio-assay is impracticable in such systems owing to the rapidity of response produced. Even fat solvents such as kerosene, which are relatively non-toxic to dipterous blowfly larvae, are rapidly toxic when presented to other insects as a relatively large external drug phase. These differences cannot be ascribed entirely to diffusion factors. Kerosene is non-toxic to blowfly larvae when injected into the haemolymph at dosages as high as 30 mg./100 mg. body weight. In fact, in the homologous series of paraffins, there is a sharp cut-off in internal and external toxicity as the series is ascended within the range C₈ to C₁₁. Below this range, rapid paralysis is induced within 1 to 2 minutes either by external or by internal drug application. Above this range, the insects survive from 1 to 3 hours. With other insects the biological "cut-off" in toxicity takes place higher in the series. Even high boiling fractions of the medicinal paraffin type produce rapid paralysis when applied externally or internally, although in systems of this type, complications arise from the rapid increase in viscosity as the series is ascended. Where the test insect is susceptible to carrier toxicity, bio-assay of drug activity becomes more difficult, and involves a reduction in the relative volume of drug phase applied to the insect externally. For example, the drug mixture may be first deposited on a porous substrate, where a proportion of the mixture becomes immobilised by absorption or adsorption processes. The deposit of drug mixture may be adjusted to form a thin film in the surface of the framework. "Film activity" may be measured by introducing suitable test insects on to the substrates which are treated with a range of deposits and drug concentrations.¹⁴ In systems of this kind, transport of the drug to the test insects is mainly influenced by the capacity of the localised drug film/test insect interface for drug transmission.

Carrier Activity of Aqueous Drug Solvents.

It has been pointed out that water has a negligible carrier activity in the presence of drugs of low molecular activity, such as ethyl alcohol. With drugs such as pyrethrins, molecular activity is extremely high, and these toxic principles form the chief basis of existing insecticidal mixtures. No synthetic insecticide has yet been prepared which approaches pyrethrins in biological activity. Pyrethrins are powerful nerve poisons, which interact specifically with the peripheral and central nervous systems of insects. The molecular structures of the pyrethrin I and II molecules are exceedingly complex, and owing to the instability of the drugs, uncertainty still exists as to the precise structure, although valuable contributions to this aspect have been made recently by Gillam and West.¹⁵

Drug reactivity depends on multipoint head group and non-polar interaction with specific receptors in the nervous system. This interaction is primarily reversible, but eventually leads to dispersion or disruption of the nerve cells, which may be shown by appropriate histological techniques. Where the carrier system consists of two miscible phases (i) an organic solvent (ethyl alcohol), and (ii) water, the bulk homogeneous carrier phase is relatively non-toxic to blowfly larvae, such as *Calliphora*, for all proportions of the components. If pyrethrins are present in this mixed carrier system, the threshold concentration of pyrethrins which induces primary symptoms of paralysis in the insect decreases as the proportion of water in the system increases.

¹⁴ This system has been used as a basis for a standard method of insecticidal bio-assay (Hurst, *Nature*, 1943, 152, 400).

¹⁵ Gillam and West, *J. Chem. Soc.*, 1942, 139, 487, 673.

The interpretation of this "aberrant" example of drug concentration-biological activity relationship is possible from some experiments which have been carried out on the Adam-Langmuir trough.¹² The capillary-active pyrethrins are only very slightly soluble in water. The drug molecules form a highly mobile "gaseous" or "liquid-expanded" monolayer at the air/water interface. This is due to the multipoint polar attraction of the orientated molecules for the water phase, and also to the small mutual cohesion of the hydrophobic portions of the molecules. The non-toxicity of a given concentration of pyrethrins in a pure ethyl alcohol carrier is due to the fact that adsorption from the organic solvent does not take place. Traube's rule does not hold for adsorption from organic solvents. The short range forces between hydrocarbon portions of molecules are much feebler than the fields of force associated with polar portions of the molecules; hence positive adsorption of a capillary active drug molecule at an organic solvent/air interface or organic liquid/liquid interface does not occur, since this would involve an increase in free energy of the system.

Since lipoids are present at the surface of the cuticle of blowfly larvae, the contact of an external water phase with the cuticle will immediately introduce a system of functional lipid/water interfaces at discrete loci on the cuticle surface. When water is added to an external drug phase consisting of a solution of pyrethrins (0.2%) in ethyl alcohol, adsorption of pyrethrins takes place at the functional lipid/water interfaces introduced into the system by the addition of water. The increase in concentration of pyrethrins presented to the insect at this two-dimensional interface is greater than the corresponding decrease in concentration in the bulk external drug mixture owing to the diluent action of water. Owing to the high molecular reactivity of the drug molecules, cuticle permeability is no longer a limiting factor in drug access at certain initial concentrations in the original ethyl alcohol carrier phase.

Biological Activity of Drugs Applied as External Two-dimensional System.

When pyrethrins are applied in an organic solvent such as kerosene, penetration of the drug through the cuticle takes place rapidly, owing to high carrier activity. The factors which influence this "induced penetration" have already been considered in other drug systems. With the following range of test insects, relative resistance (measured by application of insecticides as three-dimensional "films") increases in the order

(a) <i>Phormia terraenovae</i>	↔	(b) <i>Calliphora erythrocephala</i>	→	(c) <i>Sarcophaga falcata</i>
(adult)		(adult)		(adult)
(d) <i>Tenebrio molitor</i>	→	(e) <i>Tenebrio molitor</i>	→	(f) <i>Calandra granaria</i>
(adult)		(larva)		(adult).

When pyrethrins are adsorbed as a unimolecular film at the air/water interface, the relative activities of the drug molecules at the Gibbs' layer may be measured by using test insects as biological indicators. The insects are suspended at the Gibbs' layer, or immersed in the underlying aqueous bulk phase. By carrying out these experiments in the Adam-Langmuir trough, the concentration or activity of the adsorbed monolayer of pyrethrins may be varied experimentally by means of moveable waxed barriers. The results of such experiments have shown that (i) the biological activity of pyrethrins in the bulk aqueous phase is negligible, and (ii) the relative order of resistance of insects to pyrethrins applied as a two-dimensional film corresponds to the order of resistance when the drugs are applied as a three-dimensional phase in an organic solvent.

Pharmacological Action in relation to Fundamental Biological Pattern.

From these results the following conclusions, which are of general biological significance, may be drawn:

(1) Measurement of the biological activity of capillary active drugs by determination of the active concentrations in an aqueous carrier medium is not necessarily an indication of the active concentrations at the carrier/biological system interface owing to the possibility of selective adsorption at the functional lipid/water interfaces induced by contact of the carrier with the biological system.

(2) Wherever an aqueous phase participates functionally, or is introduced into a biological system, adsorption of capillary active drugs at biophases in contact with this aqueous phase may be a limiting factor in drug reactivity.

The general implications of these principles are immediately obvious, for lipid/protein interfaces, which are fundamentally of the oil/water type, are of universal occurrence in biological systems. The carrier activity of an external aqueous phase for pyrethrins is paralleled by the carrier activity of the internal body fluids of the insect when capillary active drugs are injected into this biophase. This accounts for the typical Traube series formed by the molecular activities of the homologous series of monohydric alcohols when injected into the haemolymph of blowfly larvae (Fig. 1 (b)). Moreover, the generalisation known as Richardson's rule, which states that for any one organism, biological activity in a homologous series of drugs increases with increase in molecular weight may be regarded simply as an expression of the escaping tendency of each successive homologue from an aqueous phase to the lipid receptors in the system. More specifically, the logarithmic relation between biological activity and length of carbon chain suggests that, in systems in which this relation holds, selective molecular interaction with an intermediary biophase is not a limiting factor in drug access, and also that biological activity is influenced by a relatively specific van der Waals' interaction of the drug molecules with the lipoids at the site of action. This relation holds for a wide range of straight chain compounds. The relatively high molecular activities of the lower fatty acids C₁ to C₆ when injected into the haemolymph of blowfly illustrate the "swamping" effect of polar interaction on non-polar interaction, and it is likely that the apparent lack of correlation between the biological activities of the lower members in homologous series of drugs and chain length is due to a similar effect, which may be accentuated when drug access to the site of action is influenced by selective molecular interaction with a bounding membrane system. These considerations help to explain the chief difficulty which has hitherto precluded a more general acceptance of the adsorption theory, namely that the parallelism between pharmacological action and capillary activity does not hold when different series are compared.

The wider implications of these principles become apparent from examination of the large body of pharmacological data which shows that, in many systems, the specific and non-specific reactivities of aqueous drug mixtures depend on drug interaction at biophases in which diffusion processes are not limiting factors in drug access. For example, immersion and micro-injection experiments on unicellular organisms have shown that narcotics and more chemically active drugs (e.g. cyanides) act specifically on the surface of protozoa such as amoebæ or paramoecia.¹⁸ When a multicellular tissue such as frog's heart is exposed to an aqueous solution of methylene blue, pharmacological action involves a surface atropine-like action which occurs before penetration of the dye into the heart cells takes place. Similarly, the antagonistic action of methylene blue on the

¹⁸ (a) Hiller, *Proc. Soc. Exp. Biol. Med.*, 1927, 24, 427, 938. (b) Brinley, *J. Gen. Physiol.*, 1928, 12, 201; (c) *Proc. Soc. Exp. Biol. Med.*, 1928, 25, 305.

specific inhibitory activity of acetyl choline occurs before the heart cells are stained by the dye.¹⁷

In systems of this kind, drug reactivity will be influenced primarily by distribution between an aqueous phase and a heterogeneous surface which is the site of action. Since it is reasonable to assume that at least some of the lipophilic elements at the site of drug action will be directly in contact with the bulk aqueous phase, the presence of this phase introduces functional lipoid/water interfaces into the system. Where the drugs are non-capillary active, interaction with the lipoid centres will depend on differential solubility between the bulk aqueous and lipoid phases. For capillary active drugs, molecular interaction will be primarily related to the work of adsorption at an oil/water interface. If the lipoid loci at the site of action are of unimolecular thickness, the distinction between differential solubility and adsorption factors tends to disappear, since the distribution equilibria in both systems will depend on drug fixation at a two-dimensional interphase.

The analogy between pharmacological action in living systems and drug phase distribution equilibria in heterogeneous oil/water synthetic systems only holds for certain pharmacological systems in which an aqueous phase is an essential component, and a diffusion process is not a disturbing influence in drug access. These simple model systems cannot be used to explain the gross divergence in drug access between corresponding homologues of alcohols and fatty acids (Fig. 1). A specificity factor is clearly involved, and the key to the fundamental nature of this factor is obtained from a comparison of a wide range of pharmacological systems. All biological systems contain protein and lipoid elements, which are functionally *fixed* structures in which physiological balance may be regulated by the functional participation of secondary biophases (*e.g.* enzymes) in the systems. Structurally, lipo-protein systems are more analogous to visco-elastic gels than to heterogeneous liquid systems.

The conception of structure in a biophase leads to the possibility of selective drug access owing to specific molecular interaction of the drug molecules with the *fixed* active or receptor groups in the bulk biophase. The drug or carrier may alter selectivity by inducing reversible or irreversible changes in the lipo-protein associations, or more specific association of the drug with the lipoid and protein components may take place so that biological activity is obscured by selective drug access. In liquid systems, selectivity is a function of drug mobility in a bulk liquid phase. Although liquid/liquid systems are of common occurrence in biological systems, the morphological disposition of these liquid biophases is primarily influenced by association with relatively fixed structural biophases. In these heterogeneous liquid-solid systems, it is difficult to assess the relative influence on drug access of the discrete component phases which are functionally inseparable. In so far as gross physical properties (*e.g.* viscosity) may be limiting factors in drug access, the conception of "functional viscosity" gives a measure of the average yield value of the biophases to drug diffusion pressure.

The establishment of the fundamental relations between biological system, drug, and carrier has depended on the choice of suitable systems. This selection was made *after* preliminary examination of other related and apparently unrelated systems. The effects of "induced drug penetration" and selective drug access are shown by a wide range of insects. With aquatic *Chironomus* larvae, penetration of ethyl alcohol is induced so rapidly by a carrier such as kerosene, that the insect swells and bursts within a few seconds after immersion in the drug mixture.

During the hardening of insect cuticle, there is a decrease in absolute and selective permeability; the relative degree of drug penetration induced by fat solvents is less than in insects with soft cuticles. This

¹⁷ Cook, *J. Physiol.*, 1926-7, 62, 160.

may be correlated with the "tanning" of the chitin-protein complex by phenolic and quinonoid substances which link or bond specific acceptor groups,^{8a, 9a, b, 18} and which results in the formation of a relatively rigid chemically-linked three-dimensional cuticle lattice framework.

As the range of biological systems is extended, it is seen that the permeability of the insect cuticle has many features characteristic of exoskeletal structures in Arthropods in general. Drug access through the cuticle of microscopic organisms such as mites is increased by non-polar solvents such as kerosene. It is interesting to notice that, even with these minute organisms, carrier toxicity of paraffins such as dodecane is relatively small. These test systems are particularly suitable for the investigation of drug reactivity, since the relatively "untanned" integument interacts readily with drugs such as amines or phenols, thereby providing a sensitive indication of the contributory influence on gross biological activity of polar interaction. Owing to the small size of these organisms, the effects of drug depletion in the external drug phase are relatively negligible. By way of contrast, the somewhat specific features of selective directional permeability which have been described by Yonge¹⁹ for the internal integument which lines the foregut of the lobster *Homarus* are, in fact, characteristic of Arthropod external integument. In this connection, there is a marked physiological analogy between the lipophil "cuticle" which lines the internal integument and the outer epicuticle of insects. Both these bounding membranes appear to be morphologically adapted to serve as regulatory selective diffusion systems.

Similar properties are shown by the integument in other groups of Invertebrates. For example, the integument of the nematode worm *Ascaris*, which lives as a parasite in the aqueous lumen of the alimentary canal of Vertebrates such as the pig, is fundamentally of the same morphological and physiological pattern as insect cuticle. The thin outer layer of *Ascaris* cuticle, which may be detached mechanically from the underlying layers, is analogous to insect cuticle. Penetration of drugs such as alcohols may be induced by carriers such as kerosene or hexane. The worms swell and burst when placed in a mixture of hexane and methyl alcohol. As the alcohol series is ascended, there is a sharp "cut-off" in selective drug access. The worms shrink owing to dehydration when immersed in mixtures of ethyl alcohol and kerosene or hexane, and a similar effect is shown with drug mixtures containing higher homologues. Shrinkage also occurs in pure ethyl alcohol. A comparison of the carrier activities of aqueous and fat solvent media reveals some striking results, which are not obvious with the more highly "tanned" insect cuticle. In the presence of water, the rate of dehydration of the worm decreases with increase of the proportion of water in the external ethyl alcohol-water mixture. In the presence of kerosene, the rate of "exosmosis" increases with increase in the proportion of oil in the external medium. These results can clearly not be correlated with simple distribution between the internal body fluids and the external drug phase, for in the ternary homogeneous mixture ethyl alcohol-kerosene-water, the solubility of water decreases with increase in the relative proportion of the oil component. An explanation is provided by analogy with the action of oils on the permeability of the insect cuticle to water. In these systems the participation of oils such as kerosene in the lipoids of the cuticle induces a decrease in functional viscosity of this phase which results in an increase in the mobility of water molecules in the outer bulk framework of the epicuticle. Molecular interaction of the kerosene carrier with the lipid centres in the *Ascaris* integument results in a similar "opening-up" of membrane lattice structure. The rate and extent of exosmosis depends on the water storage capacity of the external drug phase.

¹⁸ Pryor, *Proc. Roy. Soc., B*, 1940, 128, 378.
¹⁹ Yonge, *ibid.*, 1936, 120, 15.

The sensitivity of the *Ascaris* cuticle to changes in the external drug phase is an excellent guide to the interpretation of drug phase distribution relationships in insects. The hydrophilic protein components in *Ascaris* cuticle comprise a greater proportion of the bulk framework than in insect cuticle, and in the homologous series of alcohols, drug mobility at the functional lipoid/protein interfaces becomes a limiting factor in drug access as the alcohol series is ascended from C₁ to C₂. This "cut-off" may be demonstrated in other systems. The cuticle of the blowfly larva *Calliphora* represents a transitional stage between the relatively "untanned" *Ascaris* cuticle and the "hard" cuticle typical of adult Coleoptera. In the soft insect cuticle (e.g. *Calliphora*), the "cut-off" in the relative degree of drug access which is induced by fat solvents occurs as the alcohol series is ascended from C₃ to C₄. The hardening of insect cuticle is associated with a decrease in hygroscopicity of the protein phase, involving a reduction in functional free volume of this phase. Structurally, the hard cuticle consists of a relatively rigid open chemically-linked lattice framework which encloses the labile "bonding" phase, of which the hydrophobic lipoid components play a predominant role in cuticle permeability. As the cuticle hardens after a moult, the position of the "cut-off" in the relative degree of induced drug penetration proceeds down the homologous series of alcohols until it reaches the range C₁ to C₂. This indicates that with decrease in the van der Waals' forces of adhesion of the drug molecules to the lipoid centres in the cuticle drug mobility at the Gibbs' layer is a limiting factor in drug access which overshadows drug solubility in the bulk lipoid phase. The rapid access of the corresponding fatty acid homologue, formic acid has been discussed previously; here drug access is facilitated further by selective polar interaction with the protein phase.

When other drug systems are compared, the distinction between the soft *Ascaris* cuticle, and the hard insect cuticle, becomes more apparent. *Ascaris* cuticle is readily permeable to water—a necessary biological adaptation to the aqueous environment in which the parasite lives. The protein components interact strongly with amines and phenols, the activity of these drugs being much enhanced by the presence of kerosene, suggesting a lipo-protein mosaic structure in the cuticle. When the isolated cuticle is "tanned" by prolonged immersion in formalin or tannic acid solution, this selective permeability diminishes. This offers a marked analogy to the changes which take place in living insects during the hardening of the cuticle after a moult.

Similar factors influence drug access through pulmonary and muscle epithelia, nerve tissue linings, and similar structures in Vertebrates such as the pig or sheep. The membranes may be examined experimentally when attached to tubes to form simple osmometers.

The red cell or erythrocyte has been extensively used as an experimental system in quantitative pharmacological studies.²⁰ While the precise molecular ultrastructure of the red cell is still not clearly defined, there is evidence that the lipoid may be bound to the protein so that there is an orientation of lipoid at particular loci around the protein molecules rather than a formation of a continuous homogeneous surface layer.²¹ This suggests that the red cell envelope consists of a lipo-protein mosaic. The primary association of fat solvents with these lipo-protein centres produces reversible changes in molecular orientation of the cell surface envelope. This is shown by the reversible nature of the disc-sphere transformations which may be produced by the primary interaction of

²⁰ Ponder, *The Mammalian Red Cell and the Properties of Haemolytic Systems*, Berlin, 1934.

²¹ (a) Parpart and Dziedman, *Cold Spr. Harb. Symp., Long Island Biol. Ass.*, 1940, 8, 17. (b) Ballantine and Parpart, *J. Cell. Comp. Physiol.*, 1940, 16, 49.

(c) Ponder, *J. Exp. Biol.*, 1942, 18, 257; (d) *ibid.*, 1942, 19, 215, 220.

fat solvents with the red cell. Prolonged interaction of fat solvents disrupts or disperses the lipo-protein associations, and results in eventual haemolysis.

Further extension of the range of biological systems shows that the analogy between insect cuticle and other lipo-protein associations bridges the gap between the animal and plant systems. This parallelism is revealed from a comparison of the outer "cutinised" layer of plant epidermal tissues and the external epicuticle of insects. For example, the penetration of ethyl alcohol through the outer skin of the grape or tomato may be induced by fat solvents such as kerosene.²² Prolonged association with fat solvents produces a dispersant action which is similar to that which takes place in insect cuticle and in other animal membranes.

The range of drugs which show the effects of induced penetration in the presence of fat solvents of high carrier activity include feebly dissociating capillary active alcohols, ketones, amines, and phenols. The drugs penetrate as unionised molecules. This is in agreement with their greater activity in solvents of low dielectric constant, and is also consistent with maximum adsorption at the Gibbs' layer.

Drug access is most facilitated by non-polar fat solvents such as aliphatic straight chain paraffins, cyclic hydrocarbons such as cyclohexane, methylcyclohexane and dimethylcyclohexane, and relatively simple solvents such as carbon disulphide. These effects of carrier activity are quite distinct from carrier toxicity, which may, however, contribute to gross toxicity. Induced drug penetration is shown to a lesser degree by aromatic compounds such as benzene, toluene, xylene, pseudocumene, and mesitylene. The relative degree of induced drug penetration is still less pronounced with unsaturated aromatic carrier media such as indene or coumarone. These effects may be attributed to the fact that the aromatic solvent molecules are more polarisable than those of the aliphatic hydrocarbons, and this tendency towards capillary activity is still further accentuated with increase in the degree of unsaturation of the solvent molecules. In some systems, capillary active solvents such as oleic acid or sesame oil may reduce the carrier activity of a kerosene medium for highly reactive drugs such as pyrethrins owing to selective adsorption and blocking of the Gibbs' layer. But where an "overlap" between primary responses, such as paralysis, and secondary irreversible symptoms of joint toxic action occur, capillary active solvents may be more efficient "activators" for pyrethrins than non-polar solvents, which mainly influence functional cuticle permeability. Measurement of "activator activity" depends on a precise definition of the stage at which gross biological responses are measured.

This discussion of the fundamental analogies between different pharmacological systems has shown that correlation of biological activity with simple drug distribution between heterogeneous phases may be greatly extended if more specific factors which influence molecular interaction in monolayers are taken into consideration. In this way the more general concepts of Overton-Meyer and Traube are no longer conflicting, but may rather be regarded as expressions of molecular interaction with the biological system which become mutually related when the precise nature of the drug-biological system phase distribution relationships are defined experimentally in an appropriate range of pharmacological systems.

In conclusion, it may be pointed out that the principles which have been elaborated in the present work apply not only to drug systems applied as liquids, but also to drugs applied in the vapour phase as fumigants. It is interesting to record that the main lines of enquiry along which the present investigation has proceeded were initiated by the discovery that the non-toxic non-polar components in various samples of heavy naphtha, which is a complex mixture of coal-tar derivatives, did not "obey the

²² Hurst, *Nature*, 1941, 147, 388.

rules" by acting as diluents for the more toxic capillary active components present, such as indene, coumarone, and cresylic acids, but actually enhanced the biological activity of these components.¹ This may be attributed to the condensation and functional participation of the drugs in the cuticle framework. A transitional system between liquid and gaseous drug systems may be illustrated by the "sensitization" of insects to fumigants which takes place when the insects are subjected to a preliminary treatment of liquid non-polar solvent such as kerosene. Owing to an increase in the functional permeability of the cuticle, the treated insects respond to a lower threshold concentration of fumigant than the untreated insects.

During the course of this work, many analogies between drug access in the living insect and drug access through artificial membranes such as rubber, collodion, or gelatine have been found.²² But these analogies are only valid for a restricted range of drugs and biological systems, and become of significance when correlated with a range of pharmacological systems in which physico-chemical factors which influence drug phase distribution relationships are considered in relation to the specific physiological factors which primarily govern the nature of the biological responses produced.

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GENERAL DISCUSSION

Prof. Rideal (*Cambridge*) asked whether the morphological arrangement of the lipo-protein mosaic in insect cuticle could favour lateral drug transmission through the cuticle framework.

Dr. H. Hurst (*Cambridge*), in reply, said : It is likely that the mosaic structure of the cuticle provides a network of two-dimensional pathways which facilitate drug transmission both across and along the membrane. This may be demonstrated experimentally with pyrethrins, which are specific insecticidal nerve poisons. When pyrethrins are applied internally by injection, the drug is rapidly transported to the nerve tissues by the circulatory action of the haemolymph, and complete paralysis follows almost immediately. This is manifested by a simultaneous loss in muscular co-ordination of the limbs of the insect. External local application of the drug results in the initiation of a well-defined chain of responses : (i) local paralysis at site of application ; (ii) progressive extension of zone of paralysis ; (iii) complete paralysis, similar to the condition induced by internal drug administration.

The cuticle framework is associated with a peripheral nerve network, which communicates internally with the central nervous system. The appearance of local symptoms of paralysis following local external drug application, followed by the progressive extension of the zone of paralysis suggests that primary drug fixation involves the association of the drug with the peripheral nerve network followed by the ultimate transmission of the drug along the nerve connectives to the central nervous tissue. The rapid paralysis which follows internal drug administration can be attributed to the carrier activity of the haemolymph, in which convection ensures uniform drug distribution to the nervous tissues. Since the bulk cuticle framework is essentially a convection-proof barrier, the relatively rapid extension of the zone of paralysis following local external drug

application cannot be ascribed solely to local drug penetration through the cuticle into the haemolymph followed by convection transport in this substrate, a process which would favour rapid simultaneous paralysis after the initial penetration of the drug through the cuticle had taken place. Neither can the progressive nature of the biological responses produced be explained by lateral drug diffusion through a cuticle framework in which discrete lipoid channels run transversely across the cuticle, since the two-dimensional lipo-protein discontinuities in this direction would involve a relatively slow three-dimensional diffusion across intermediary lipoid or protein phases.

This evidence indicates a continuity of lipo-protein interfaces along the membrane framework. The relatively abrupt morphological transition from a lipoid-rich epicuticle outer layer to the underlying hydrophilic chitin-protein layer would also favour selective adsorption and two-dimensional drug diffusion along the outer layer of the cuticle framework.

It is interesting to note the analogy between the insect cuticle and the bounding membranes of nerve fibres, where the presence of bounding layers of radially orientated lipoid molecules provides a pattern of interfaces which would favour rapid drug transmission along the outer nerve sheath.²² In addition, the effects of induced drug access which may be obtained with isolated nerve sheath preparations suggest that narcotic action may well be associated with the reversible functional changes in free volume of the lipoid centres; in this way corresponding changes in the capacity for ionic transmission of the nerve sheath, or in more specific molecular orientation of active patches would influence normal irritability. This simple conception conforms well with a large body of experimental data which shows that similar narcotic action may be produced by fat solvents of diverse chemical composition.

²² Schmitt and Bear, *Biol. Rev.*, 1939, 14, 27. Schmitt and Palmer, *Cold Spr. Harb. Symp., Long Island Biol. Ass.*, 1940, 8, 94.

SOME PHYSICAL CHEMICAL PROPERTIES OF BIOLOGICALLY ACTIVE MOLECULES.

By J. H. SCHULMAN.

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(a) *The physical chemical properties* that will be chiefly dealt with in this paper are those governed by short range forces, such as polar association or induced polar association as designated by Van der Waals forces.

These are the forces that become primarily involved when one molecule approaches another situated in a structure as in a membrane or site of action as in a nerve sheath, or by direct association in a plasma, or furthermore are directly responsible for the structure and viscosities of the membranes or plasma themselves. These forces are governed very simply by Coulombs' law and for the non-polar or induced polar forces by London's theories. Overton and Meyer on oil solubility and Traube on surface activity of molecules in relation to their biological activity are specialised aspects of this theory.

(b) *Biological activity* as described here is related to the concentration in which a certain chemical produces a standard biological response, there is thus a time factor which also has to be standardised. Enhancement of the activity by means of mixtures or adjuvants will not be discussed here. The chemicals which will be chiefly discussed are those that are lipoidal (hydrocarbon) in nature or possess a large hydrocarbon group, or proteins or mixtures of both, i.e. lipo-proteins. Although the physical chemical

properties which will be discussed in detail refer equally well to a lipoidal as to a protein molecule, the chemicals discussed will be divided into the above categories.

There are a number of complicating factors in assessing biological activity of a molecule which must be carefully sorted out before applying any rules to any specific system. For example, a molecule may have to penetrate a membrane, or associate with another molecule (carrier molecule) before reaching the site of action, or the molecule having become dispersed in the reacting system by the above means then has to be reacted upon by ferments, and it is the break-down products which produce the reaction. So a molecule may have to contend with membrane permeability, dispersion in the system by complex formation with a carrier molecule, or adsorption on to a colloid carrier (*i.e.* emulsion interface) and then attack by a ferment to form the actual reacting chemical *in situ* where it is required. A great number of molecules the chemistry of which will be discussed, answer in one way or another to the above criteria.

Dr. Hurst gives a good example of the effect of penetration of a membrane using certain insects as a test mechanism. The insect may either be immersed in the chemical or the chemical be injected into the insect, thus eliminating the effect of the membrane, or it is possible to treat certain chemicals like the cancer-giving hydrocarbons which would appear from the physical chemical behaviour to be inert biologically, with ferments or U.V. radiations *in vitro* and obtain the biological action from the break-down products. Thus it is possible to separate to a certain extent the various factors other than dispersion or carrier, which go to make up the standard biological response.

Physical Chemical Characteristics.

The chemical groups involved in association between molecules are the hydrocarbon groups, polar groups and the ionic groups. Automatically the spacing and stereochemical interrelations between these groups must and can be shown to play a very important part in the resultant force of association between the molecules. The associating forces are directly proportional to $1/r^2$, $1/r^4$ and $1/r^6$ (r = distance between groups) respectively (and $1/r^8$ for an ion dipole association). This shows how sensitive the association forces are to mutual orientation and adlineation between the molecules, thus any slight change in ionisation, dipole charge, number of carbon atoms, distance and spacing between the associating groups can make or break a complex, thus giving them their high degree of specificity. The monolayer technique (surface potentials and surface pressures) is a very convenient tool to measure the associating forces between all these groups in great detail, and it can be quickly shown that the interactions measured at the interface also take place in three dimensions. An interface is convenient for measuring these forces owing to the strong asymmetrical field which separates the polar from the non-polar groups, thus allowing them to interassociate, either inter- or intra-molecularly.

It can be shown that an alipathic hydrocarbon chain of $18(\text{CH}_2)$ is approximately equivalent in force of association with another hydrocarbon chain, both in the trans configuration, as an ion dipole association, both being of the order of 15,000 cal. The hydrocarbon association is markedly weakened when CH_2 groups are arranged in the cis form, thus preventing adlineation between the hydrocarbon chains. Likewise the polar association is broken down when polar groups are changed, for example from a SO_4^- ion with an $-\text{OH}$ dipole to an $-\text{OOCCH}_3$ polar group, or NH_3^+ with an OH polar group to an $\text{N}(\text{CH}_3)_2^+$ with an OH polar group. The methyl groups in the latter case keeping the ion from approaching the OH polar group as close as in the unsubstituted case. On the other hand, the methylation will increase the ionisation of the amine polar groups in

alkaline solutions, thus in certain circumstances greatly increasing the interaction of the amine polar group in spite of steric hindrance. Methylation is known to have marked effects on biological activity of certain molecules. This can be due to an easier break-down of the molecule by ferment in its methylated form.

Examples of complex formation between large molecules as measured by the film technique and how they have direct bearing on associations between the molecules in solution give useful analogies as to a possible biological function of the interacting molecules. They give also a good indication of the meaning of the discrepancies found with Overton and Meyer and Traube theories for a series of homologous compounds. For example, at a restricted interface of a long chain alcohol or an alcohol such as cholesterol where the sodium salt of a long chain sulphate is injected into the underlying aqueous phase, an interfacial tension of some 5 dynes/cm. can fall 50 dynes in a minute, although the soap by itself at this concentration (1 mg./250 cc.) will only change the interfacial tension some 10 dynes/cm. over a period of 30 minutes. This change in interfacial tension is also accompanied by great changes in interfacial viscosity. This phenomenon can be shown to be due to the water soluble long chain paraffin ion penetrating into the alcohol monolayer and forming an equimolecular mixed film. This interfacial film on compression collapses as a unit without ejection of either component from the interface. Should the association be broken down by a simple esterification of the alcohol polar group or a *cis*-double bond being formed in the hydrocarbon chain only very weak penetration of the monolayer takes place. The penetrating molecule in this case being easily ejected on compression of the interface back into the aqueous solution or surface lens or crystal. There is in this case only negligible alteration of the interfacial tension. Should, furthermore, the prospective penetrant have two polar groups which are spaced by the hydrocarbon portion of the molecule and are reactive with the interfacial forming polar groups, then no penetration of the interface takes place, but the aqueous soluble molecules adsorb onto the film forming molecules by means of the polar association, and thus form a duplex or double layer. This form of association does not change the interfacial tension, but radically alters interfacial rigidity or elasticity. With large complex molecules both these phenomena occur and examples will be given where slight changes in the chemistry of the compound, an adsorbing molecule can be changed into a penetrating one, with subsequent radical change in biological activity.

Complexes in Bulk Solution.

For the above-mentioned examples similar radical changes can be shown to exist for the behaviour of the associating compounds composed of hydrocarbon and polar groups both in the aqueous and oil phases.

For example, a long chain hydrocarbon alcohol is insoluble and inactive in water but is readily dispersed into water when mixed equimolecularly with a long chain paraffin ion. This can be shown chemically by inhibition of the precipitation compounds of the soap and biologically by a 100% increase in the lytic activity of a soap solution by the presence of the long chain alcohol. The reverse of this phenomenon can take place if cholesterol be now substituted for the alcohol; the lytic activity of the solution being completely inhibited. As can be expected no effects are noticed when the OH polar group is esterified. A further biological analogy is worth noticing here, if bacteria which are unaffected by saponin be incubated with cholesterol lysis of the bacteria takes place. A similar phenomenon takes place if oil is the continuous phase, an oil insoluble long chain paraffin ionic salt is readily brought into dispersion or solution in the oil phase in the presence of an equimolecular concentration of a long chain alcohol or other associating molecule. This solution of a soap or

other poorly soluble oil compound into an oil phase can bring about great changes in three dimensional viscosity.

This system can work even if the associating molecules are the ionised and unionised form of the molecule, for example in half dissociation. Thus oleic acid will readily disperse sodium or calcium oleate into oil.

One may now see how the partition coefficient of a molecule soluble in both phases may be radically altered by the presence of an oil or water soluble interacting or complex forming molecule present at least in equimolecular concentrations. Or even bring into either oil or water solution and thus into biological activity an insoluble molecule by means of complex formation. These concepts must be taken into consideration, when theorising on the Overton-Meyer oil solubility rule for drugs, and possibly explains many puzzling discrepancies found hitherto.

In an even more striking manner can the discrepancies with the Traube theory be clarified. Thus in the previously given example of how the great change in surface tension of an aqueous solution of a long chain paraffin ionic salt can be brought about by the presence of a monolayer of an aliphatic alcohol or cholesterol, which furthermore can be eliminated by small changes in the chemistry or stereochemistry of the alcohols; then the surface activity of a compound must be made analogous to its drug action or biological action only at the interacting interface. As shown above the interfacial tension can change some 50-60 dynes/cm. for the same compound at interfaces composed of molecules varying only slightly in their chemistry.

It has been shown by Schulman and Rideal that the lytic activity of a series of surface active long chain paraffin ionic salts bear relation only to their surface activity at a cholesterol or protein interface and in no way to their surface tension lowering of an aqueous solution.

Optimum Activity of a Homologous Series.

It is a general characteristic of a whole range of biologically active compounds that in their homologous series a marked optimum of biological activity is noticed. A series may vary only in the changing number of (CH_2) groups or polar groups, and their mutual spacing or position of a substituting methyl group.

It has been remarked here that the interfacial activity or associating force of a molecule acts on its reactive site in two pronouncedly different ways. The molecules may firstly penetrate an interface forming a mixed interfacial layer or disperse the molecules into their otherwise antagonistic phases, thus causing lysis or enhanced or inhibited activity of the molecule by association, or secondly adsorb on to the interfacial layer, thus tanning the interfacial molecules or causing agglutination of the colloids or cells whose interface has thus become acted upon.

It has been shown by Schulman and Rideal that the optimum of activity of a homologous series can take place at the change over of a molecule from its adsorbing properties on a specific system to its dispersant properties. Thus with the synthetic oestrogenetic compounds $\beta\beta'$ dihydroxy stilbenes varying only by a (CH_2) the optimum biological activity takes place at the compound's most active adsorbing form on a protein interface, the activity immediately declining again on the molecule showing dispersant action on the interfacial protein molecules. The optimum lytic and haemolytic activity of a series of surface active compounds varying in number and position of (CH_2) groups and nature and number and mutual spacing of polar groups is at the optimum dispersant action of the molecules on a cholesterol or protein interface. Dr. Hurst will be describing similar optima based on these two conceptions for a homologous series of simple alcohols and acids in their drug action on insects.

Similar analogous optima have been described by Schulman and

Rideal for the cancer-giving hydrocarbons, but in this case it is related to the labile break-down products of the molecules caused by U.V. irradiation in certain organic solutions, and their consequent adsorption on to protein interfaces.

Thus the Traube conception of surface activity and the Overton-Meyer conception of oil solubility must be related to the active compounds associating with the specific interacting interface and not generalised for surface activity at an air water interface or oil not in the presence of other oil soluble compounds.

Molecular Orientation and Biological Activity.

Lipo-protein Associations.—It is known that most proteins will spread at air water or oil water interface, or can be made to spread at any aqueous oil interface by suitable dispersion in solvents (alcohols and salts) and suitable charging of the oil interface. It is evident that the protein molecule has undergone some radical change in the process of spreading at the oil water interface, since it is now in an insoluble form. It is presumed that the protein molecule in aqueous solution is a colloid nearly globular in shape, kept in solution or dispersion by means of the ionic and polar groups being orientated into the water phase and the non-polar portions being associated and orientated towards the centre of the colloid. Upon arrival of this molecule at the oil water interface, these various groups in the molecule are separated and reorientated owing to the asymmetric field at the interface.

Thus a protein molecule spread at an interface has its various groups orientated in a triplex layer. The non-polar side chains being pulled into the oil phase and the ionic polar groups pulled into the aqueous phase with the polar keto-imido group in the polypeptide backbone separating the ionic from the non-polar groups. This adlineation of the various groups in the molecule permits them to associate by the short range forces already described either inter- or intra-molecularly.

If these inter-associating groups are small in number per molecule or the molecular weight is relatively small, the protein molecule can be squeezed back into the aqueous solution by means of two-dimensional compression of the interfacial film. With molecules of large molecular weight collapse and fibre formation occur before the molecules can be redispersed. Quite a different picture presents itself if the protein is mixed with lipoids or adsorption of the protein molecule takes place at a lipoid or charged oil water interface, the process now being reversible. The charge being made possible by spreading hydrocarbon ionic compounds, such long chain amines, carboxyls, sulphates, lecithin, cephalin (*psychosin*, *sphingo-myelin*) and allied compounds at the oil water interface. Precisely analogous phenomena now occur as described with the salts of hydrocarbon ionic compounds, the protein may adsorb as a double layer on to the lipoid interface or penetrate the interface to form a mixed lipo-protein monolayer, thus greatly changing the interfacial viscosity and rigidity and surface pressure, or the protein molecule may be repelled from the interface by like electrical charges. The great difference between protein and lipo-protein films is that on compression of the mixed film, the protein molecule is ejected from the mono-layer back into the aqueous solution in the form of double layer again, this process being reversible. If now to a lipin-protein mixed film excess lipin be added to the aqueous solution, the protein is completely displaced from the interface and redispersed into the aqueous phase. What form this redispersed protein has taken is of great interest and attempts are being made by use of biologically active molecules to investigate this point.

Frazer, Stewart, Elkes and Schulman have recently shown that most of the phenomena occurring at the oil water interface as described above can

be strikingly demonstrated by means of oil in water emulsions. The oil water interface can be readily charged either negatively or positively by means of negative stabilising agents such as salts of long chain sulphate, carboxylates, and positively by salts of long chain amines and substituted amines. The adsorption of the protein will take place according to the pH of the aqueous solution in relation to its isoelectric point, and the sign of the charge on the stabilised oil droplet, together with its zeta potential as controlled by the salt concentration of the aqueous phase. When adsorption takes place the oil droplet is electrically discharged and is surrounded by a rigid or elastic protein monolayer, these neutral droplets can thus agglomerate or agglutinate into bunches and, owing to their density sediment to the top of the aqueous solution. Thus, if protein be added to a stabilised emulsion and the conditions are correct for adsorption, agglutination of the oil droplets takes place with subsequent clarification of the aqueous solution at a protein concentration which is sufficient to cover the surface of the oil droplets with a monolayer. If polyvalent cations or anions be added to the agglutinated emulsion, the agglutination is broken down owing to the removal of the stabilising agent and an oil layer separates out on top of the aqueous solution and the protein is redispersed into the aqueous solution. A similar effect can be achieved by adding excess stabilising agent to the system, the protein coating around the oil droplets being thus deterged away from the interface and protein molecules are redispersed.

The conditions for adsorption of the serum proteins have been demonstrated; thus serum albumin will adsorb on to positive oil water interfaces above its isoelectric point of pH 4.6 and not below this pH , and on to negatively charged oil water interfaces at pH 's below its isoelectric point and not above.

This switch-over from adsorption to no adsorption of the protein with pH of the aqueous phase is very sharp at low salt concentrations. Equally, serum globulin will adsorb on to positively charged oil water interfaces above its isoelectric point of pH 6.8 and not below and on to negatively charged interfaces below pH 6.8 and not above. The sharpness of the change over is less with increasing salt concentration and size or molecular weight of molecule. It is now interesting to note that between pH 4.6 and pH 6.8 the isoelectric points of the two proteins mentioned, serum albumin will adsorb on to a positive interface and serum globulin on to a negative interface. Thus the proteins can be preferentially adsorbed on to a charged interface from a mixed solution, salt concentration also playing a role in the adsorption.

Frazer and Stewart have shown that when bacteria toxins, snake venom or hormones such as insulin are adsorbed on to emulsions they are not active when injected into animals, but that when the emulsion is broken either *in vivo* or *in vitro* and the protein molecules are redispersed from the oil water interface into the aqueous solution full biological activity returns. This suggests that the protein molecule orientated at the interface is in an inactive form, but can be redispersed into solution and biological activity, when associated with lipoids or lipins.

Likewise, it can be suggested from the first section of this paper that the biological activity of the lipoids and lipins is radically altered when in association with other lipoids, as well as with the proteins.

It can be further suggested that the principles of the short range forces discussed in this paper on the association between lipo-proteins and the influence of other lipoids or chemicals or drugs on these associations will help to clarify some of the actions *in vivo* of drugs.

A POSSIBLE MODE OF ACTION OF BENZPYRENE AS A TYPICAL CHEMICAL CARCINOGEN.

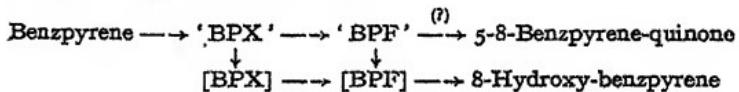
By F. WEIGERT.

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An outstanding feature of the chemical carcinogens is their long delayed action. When the skin of mice is painted with a great excess of the dissolved carcinogen the first tumours do not appear until many weeks, and even months have elapsed. The latent period can be interpreted by biological conceptions, which include the various precancerous states of the tissue until a normal cell is transformed into a malignant cell. We are interested here in a physico-chemical study of the problem whether the carcinogenic drug or one of its metabolites can persist within a living animal over periods which are commensurable with the latent period, and whether it is liable to a spontaneous transformation which may stimulate the change of the cell race. Experiments at the Mount Vernon Hospital have been in progress during the last four years.¹ Benzpyrene was chiefly studied, although it is not the most potent carcinogen, because it is distinguished from other carcinogenic hydrocarbons by a number of different typical fluorescence and absorption spectra.

From the experiments of Peacock, Chalmers and Berenblum and their collaborators² it follows that by far the greater part of the benzpyrene which has been introduced into a mouse or rat is changed to non-fluorescent derivatives which have not yet been accounted for. About 1% is excreted unchanged and the rest appears as blue-fluorescent 'BPX' in the bile and is excreted in the faeces as 5-8-benzpyrene-quinone and as green-fluorescent 'BPF' from which 8-hydroxy-benzpyrene could be isolated.

This metabolism has now been followed in greater detail by fluorescence- and absorption-spectrography and by fluorescence-chromatography which led to the following tentative scheme:



[BPX] and [BPF] are prepared by fluorescence-chromatographic purification of extracts from 'BPX' and 'BPF' respectively, from which they are distinguished by their fluorescence spectra.

The blue-fluorescence spectrum of 'BPX' can be seen in the skin, liver, lung and kidney-cortex after application of benzpyrene to a mouse or rabbit. Furthermore, it appears in the bile and small intestine which are the chief route of excretion, and in the milk in the stomachs of suckling mice after intravenous injection of benzpyrene into the mother. Green-fluorescent 'BPF' appears in the alimentary canal beyond the ileo-caecal valve, in the bladder-urine, and together with 'BPX' in discrete patches of the lung.

¹ Weigert, *Trans. Faraday Soc.*, 1940, 36, 1033; *Nature*, 1942, 150, 56; Weigert and Mottram, *Nature*, 1940, 145, 895; 1942, 150, 635; *Chem. Ind.*, 1941, 60, 617; *Biochem. J.*, 1943, 37, 497; Doniach, Mottram, and Weigert, *Brit. J. Exp. Path.*, 1943, 24, 1, 9.

² Peacock, *Brit. J. Exp. Path.*, 1936, 17, 164; *Amer. J. Cancer*, 1940, 40, 251; Chalmers, *Biochem. J.*, 1938, 32, 271; Chalmers and Crowfoot, *ibid.*, 1941, 35, 1270; Berenblum, Holiday and Schoental, *Cancer Res.*, 1943, 3, 145, 151.

[BPX] and [BPF] are different with respect to their spectrographic and chromatographic behaviour:

(1) The blue-fluorescence spectra of [BPX] show the same banded structure as adsorbate on alumina and as eluate in alcohol. The fluorescent zone remains fixed at the top of the column even after long development.

(2) The green-fluorescence spectrum of the adsorbate of [BPF] on alumina shows no bands, but the blue-fluorescence spectrum of its eluate in alcohol has a banded structure. The fluorescent zone of [BPF] on alumina moves slowly down during development.

(3) The absorption spectrum of [BPF] in alcohol is very similar to that of 8-hydroxy-benzpyrene, while that of [BPX] is unrelated to any known benzpyrene derivative.

(4) Apart from these chief differences, minor distinctions can be seen according to the origin of the preparations. For instance, the blue-fluorescent zone of [BPX] at the top of the alumina column is narrow and sharp with extracts from bile and small intestine, but extended and diffuse with extracts from liver, while those of kidney-cortex and lung are diffuse but less extended. The diffuse green-fluorescent zones of the adsorbates of [BPF] which move down on development are not so typical, but the fluorescence spectra of their eluates in alcohol show slight displacements of the bands according to the origin of the extracts.

These results show that 'BPX' and [BPX], on the one hand, and 'BPF' and [BPF] on the other hand, comprise two groups, the X- and F-groups respectively, the members of which contain two different benzpyrene derivatives as prosthetic groups combined with various cell constituents. The fluorescence spectra of the adsorbates of the X-group give evidence that the carrier molecule is adsorbed by the alumina, and that the benzpyrene-group is not affected optically by the adsorption. In the F-group the disappearance of the fluorescence bands in the adsorbate indicates that the adsorbed portion of the molecule is the benzpyrene group itself, which is probably identical with 8-hydroxy-benzpyrene.

All members of the X-group are metastable and are readily transformed into members of the F-group. This happens *in vivo* when bile-'BPX' passes through the ileo-caecal valve into the caecum and when kidney-'BPX' enters into the urine. In the lung it occurs apparently in the 'BPX'-holding cells themselves. Post-mortem it can be seen with all 'BPX'-containing tissues, if they are kept for some time at 37°, and even after three days in the ice-chest. This transformation is obviously due to autolysis and to a detachment of the carrier molecules. It can be completely prevented by formalin and other preservatives. [BPX] which is adsorbed on alumina is transformed into [BPF] at elevated temperature *in vacuo*.

There is no direct evidence whether the 5-8-benzpyrene-quinone is produced directly from 'BPX' or via 'BPF'.

'BPX' appears and is fixed just in those tissues, skin (where it persists in the Malpighian layer for over three weeks), lung and liver, where tumours can be produced by benzpyrene. Hence it is likely that its metastability and its spontaneous transformation into 'BPF' according to the laws of probability may be the reason for the stimulation of the change of a normal into a malignant cell.

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SOME MORPHOLOGICAL AND OTHER VARIATIONS IN A STRAIN OF BACT. LACTIS AEROGENES ACCOMPANYING ITS ADAPTATION TO CHANGE OF MEDIUM.

By R. M. LODGE AND C. N. HINSHIELWOOD.

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Certain relevant conclusions from previous studies of the growth of *Bact. lactis aerogenes* will first be summarised.

1. The maximum population, n_s , which a given medium will support depends partly upon the power of the cells to remove by oxidation inhibitors formed during growth.¹

2. In an artificial medium consisting of ammonium sulphate, glucose, potassium dihydrogen phosphate and magnesium sulphate (v. p. 432), young inocula show a lag phase, referred to as "early lag," during which a growth promoter is formed, diffuses into the medium and stimulates growth of all the cells. This substance is referred to as (L).²

3. When *Bact. lactis aerogenes* which has been grown in bouillon is transferred to the above artificial medium, long snake-like cells, up to 20 times the normal length, are formed if the glucose concentration lies between certain limits. The size distribution of the cells approximately follows the law $n_l = n e^{-l/\bar{l}}$ where n_l is the number of cells of length greater than l , n the total number and \bar{l} the mean length. The interpretation given is that we are dealing with a condition where division is delayed: the probability of division is here the limiting factor, whereas normally the elongation of the cell is rate determining.³

A size coefficient, σ , is defined by the relation $\sigma = \sum_{l=3}^{\infty} l \cdot v_l$ where v_l is the number of cells in unit range in the neighbourhood of l (measured in certain arbitrary units). σ gives a good representation of the abnormal or "snake-like" appearance of the culture. During the growth cycle it rises to a maximum and then falls, often to zero.

The influence of various factors, including filtrates from older cultures, on σ leads to the hypothesis that there are two independent factors referred to as (L) and (D) which control elongation and division of the cells respectively.

With successive subcultures of the organism σ varies in such a way as to suggest that the enzyme systems responsible for the (L) and (D) factors are easily thrown out of balance, and that by a slow process of adaptation they can be brought into balance again. A theory of this adaptation is given by Hinshelwood and Lodge in the paper referred to.

Bact. Lactis Aerogenes (Morris).

This was a strain obtained from the National Collection of Type Cultures (Number 5268) and differed from that used in all previous work in that it had, in the glucose-ammonium sulphate medium, a much slower growth rate (m.g.t. of about 120 minutes, compared with the normal 32 minutes), and at first grew with a long lag to a small value of n_s .

On repeated subculture in artificial media, after transfer from bouillon (heart broth), it showed remarkable phenomena of adaptation. n_s pro-

¹ Lodge and Hinshelwood, *J.C.S.*, 1943, 208.

² *Ibid.*, 214.

³ Hinshelwood and Lodge, 1943, *P.R.S., B, in the press*.

gressively increased to many times its initial value and the (D) and (L) producing functions first of all became increasingly unbalanced—as shown by the production of long snake-like cells—and later came into normal relation once more—as shown by the elimination of these snake-forms.

We conclude from this that the three functions of the cell, (a) the oxidation of inhibitors (*v. para. 1, above*), (b) the synthesis of the lag remover, (L) (*v. para. 2, above*) and (c) division, are all adapting themselves to the new medium at separate and independent rates.

It follows that the three functions which are here revealed as independent should themselves be susceptible to separate control, e.g., by drug action. Several kinds of observation can be correlated from this point of view. For example, (a) pH can affect n_s without affecting m.g.t.⁴ or lag.* (b) lag can be prolonged or reduced independently of m.g.t. or n_{s_4} .⁵ (c) snake-like forms can be induced by chemical agencies⁶ in such a way as to indicate that the division function is specifically impaired.

In what follows, the behaviour of the strain "Morris" of *Bact. lactis aerogenes* leading to this conclusion is described.

A. Serial Subcultures in Artificial Media.

Bacteria were transferred from a stock bouillon culture to aerated artificial media, and subcultures, using 1.0 cc. inocula for 26.0 cc. of fresh artificial medium, were made every 48 hours. The media contained as nitrogen source ammonium sulphate, the equivalent amount of an amino acid (asparagine or alanine), or a mixture of ammonium sulphate and an amino acid. The mixture was originally used because growth in ammonium sulphate was difficult, and it was thought that the cells could be trained to use it by a gradual reduction to zero of the amount of amino acid in a mixture with ammonium sulphate. The course of training, however, proved to be more complex than expected.

Fig. 1, for a typical series of subcultures in a medium containing a constant mixture of ammonium sulphate and asparagine as nitrogen source, shows the course of the adaptation from bouillon to this medium. (Here, n_{s_4} refers to haemocytometer counts of samples taken 48 hours after inoculation. The value of n_{s_4} does not differ significantly from that of n_s in the same culture. Values of σ_{s_4} greater than about 20 indicate that a culture has a definitely abnormal appearance—*v. para. 3 above*.)

It should be noted that n_{s_4} , the logarithm of which is plotted in Fig. 1, starts at a small value and increases steadily to a limit as the serial subculture number is increased. Upon subculture for the fourth time, when the maximum population has attained almost to the limit, σ_{s_4} rises sharply

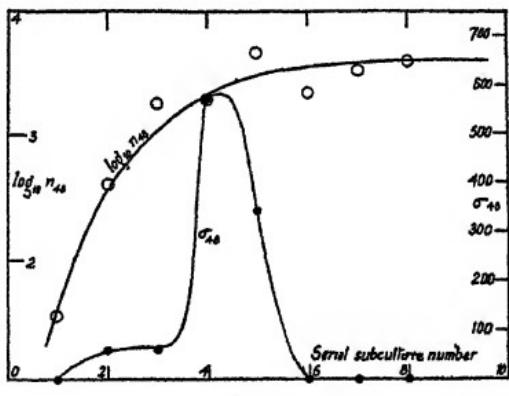


FIG. 1.

* Lodge and Hinshelwood, *J.C.S.*, 1939, 1683.

† Unpublished observation.

‡ Cf. Lodge and Hinshelwood, *J.C.S.*, 1939, 1692.

§ Cf. p. 428, and also Hinshelwood and Lodge, ref. 3.

to the high value of 580 and the culture shows a remarkable appearance. It is clear that the division function has become quite out of balance with the elongation of the cells at this stage; this is, according to our hypothesis, due to the development of a corresponding lack of balance between the (L) and (D) factors. The balance is nearly restored after the sixth subculture, though long cells occur sporadically during many subsequent ones.

There has been a development of the power of the cells to multiply to a high n_{48} : there has also been development of their capacity to elongate and to divide in the new media. All these processes seem to have evolved independently and at different rates.

Qualitatively similar behaviour is shown by successive cultures of the organism in media containing as nitrogen source a mixture of ammonium sulphate and alanine, asparagine alone, or ammonium sulphate alone (Table I). At some stage in a series, after n_{48} has become more or less

TABLE I.

Serial Subculture Number.	Ammonium Sulphate.		Asparagine.		Ammonium Sulphate + Asparagine.		Ammonium Sulphate + Alanine.	
	n_{48} .	σ_{48} .	n_{48} .	σ_{48} .	n_{48} .	σ_{48} .	n_{48} .	σ_{48} .
1	188	0	36	0	33	0	108	0
2	Tangle		80*	0	400*	60	18	0
3	Tangle		Tangle		1900	60	256	0
4	Tangle		1200	580	3000	580	700	200
5	2760	870	1500	25	4800*	350	480	200
6	3500	50	2600	15	2200	0	800	0
7	4000	100	1400	48	3600	0	360	10
8	4500	30	1000	27	4000	0	340	28

* Transfer from these cultures into ammonium sulphate media gave tangles.

stabilised, cultures begin to assume a thread-like appearance which, on further subculture, eventually disappears.

Sometimes, at certain stages in a series, the cells clump together to such an extent that counting becomes impossible. This must depend upon another function which seems to develop independently, but, from its nature, it does not lend itself to quantitative measurement.

If, in a given series of subcultures, the inoculum size is reduced to a tenth, at a stage when adaptation is just complete (as shown by stabilised behaviour in successive subcultures) a certain regression occurs and snake-like forms re-appear. Sudden reduction of the inoculum size can thus cause an upset of the enzyme balance, which must depend upon indirect effects—changes in lag (*v. para. 2, above*), concentration of growth promoters in the medium, and so on.

B. Transfer from Media with Amino Acid as Nitrogen Source to Media with Ammonium Sulphate.

When *Bact. lactis aerogenes* (Morris) is transferred from bouillon to artificial media, there is a drop in n_{48} from 800 to about 100. On further subculture in the artificial medium, n_{48} reaches several thousands. There can, however, be a much more striking change when the organisms are transferred from a medium containing an amino acid nitrogen source to one containing ammonium sulphate.

If a culture grown several times in media containing amino acid mixed with ammonium sulphate is transferred to one with ammonium sulphate alone, growth in the latter appears under the microscope as a tangled skein of threads of almost indefinite length. The culture is remarkable for the

complete absence of cells of normal size; the division probability seems to be practically zero. A second subculture in ammonium sulphate may show this phenomenon even more markedly, but, on continued cultivation in ammonium sulphate, the cells tend to become normal once more, although some very long cells may still appear after eleven subcultures (*v. C.*, below).

It would seem that, in the media containing a mixture of asparagine or alanine with ammonium sulphate, the bacteria become adapted to use the amino acid rather than the ammonium sulphate. We already have evidence (Hinshelwood and Lodge)³ that (D) is formed easily in amino acid media; in such media there will be little development, therefore, of the mechanism by which (D) is produced in ammonium sulphate media. Accordingly, when the cells are deprived of amino acid, the (D)-forming function may be very deficient, and adaptation to growth on ammonium sulphate must occur. The transient derangement of the enzyme balance is at first so great that it leads to the appearance of the tangled threads.

The phenomenon is not easy to reproduce. It can occur as well with the third as with the fifteenth subculture in the mixture on transfer to ammonium sulphate, but it varies somewhat erratically with the age of the culture before transfer.

C. Size Distribution of Cells.

Reference was made in paragraph 3 to the logarithmic size distribution of the cells of the ordinary fast-growing strain of *Bact. lactic aerogenes* grown in the artificial medium at certain glucose concentrations.

TABLE II.—NITROGEN SOURCE OF INOCULANT: AMMONIUM SULPHATE + ASPARAGINE. INOCULATION INTO AMMONIUM SULPHATE MEDIUM.

Size Range.	Number of Cells in the Range.	
1/2	130	
1	132	Rapid decline, probably following logarithmic law.
2	72	
3	26	
4	0	
5-10	37	
10-15	36	
15-20	16	
20-25	16	
25-30	3	
30-40	3	

TABLE III.—DECLINE OF THE SNAKE-LIKE FORMS ON SERIAL SUBCULTURE IN AMMONIUM SULPHATE OF THE CULTURE ANALYSED IN TABLE II.

Serial subculture number:	1	2	3	4
Size Range.	% Bacterial Substance in the Size Range.			
0-2	18.2	—	60.6	70.5
2-5	10.0	—	21.2	17.4
5-10	13.5	—	10.4	9.6
10-25	48.4	—	7.8	2.5
25-40	9.9	—	0	0

Generally similar distributions are shown by the "Morris" strain, except when the tangle of threads appears. The size distribution is then different. Over the range of smaller sizes ($l = \frac{1}{2}$ to 4) the logarithmic law is approximately followed. There is, however, in the larger size range ($l = 5$ to 40) a secondary distribution with a different law.

Table II gives numbers showing this for a culture growing in ammonium sulphate and inoculated from an asparagine-ammonium sulphate mixture. When grown, the transferred culture contained many long cells, but was not a tangle of the most marked kind. On further subculture in ammonium sulphate, the frequency maximum receded to the smaller size ranges, as shown in Table III.

It is not proposed to discuss the size distribution in detail. It will only be remarked that the distribution in the longest size ranges may be

determined more by the mechanical snapping of threads which might have reached an indefinite length than by the division probability, which may well approach zero.

Summary.

When a certain (slow-growing) strain of *Bact. lactis aerogenes* is transferred from a given medium to one of a different kind and is subcultured many times in the latter, the stationary populations attained and the morphological variations occurring in successive subcultures indicate that the individual cell functions responsible for (a) removal of growth inhibitors, (b) elongation and (c) division are all undergoing adaptation independently and at different rates.

In certain circumstances (b) and (c) may become so unbalanced that thread-like cells of enormous length are formed.

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THE EFFECTS OF RESORCINOL AND OF *m*-CRE-SOL ON THE GROWTH OF *BACT. LACTIS AEROGENES*.

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A study of the influences of disinfectants on bacteria may be expected to shed light on the numerous chemical reactions involved in life processes.

To this end, the effects of resorcinol and *m*-cresol, as part of a series of phenols, on the growth of *Bact. lactis aerogenes* in a liquid artificial medium have been investigated. It has been found that the duration of bacterial lag, the growth rate and the stationary population to which the culture attains are all influenced by the presence of disinfectant. The precise relationships between each of these quantities are not, however, identical, indicating that these disinfectants act by retarding particular cell reactions rather than by exerting a general depressant effect on metabolism.

Bacterial lag varies with the age of the parent culture. With the particular organism and medium used in this work it has been shown¹ that there is a considerable lag (known as "early lag") when the inoculant itself has just started to grow. As growth of the inoculant proceeds, the lag first falls to a minimum and then increases ("late lag") on further ageing of the inoculant. The variation of early, minimum and late lags with disinfectant concentration has been studied.

The rate of bacterial growth is inversely proportional to the mean generation time (m.g.t.), which is the time taken for the population to double. Results are expressed as the ratio of the value of the m.g.t. for a culture containing no disinfectant to that obtained in the presence of disinfectant. Stationary population (n_s) is defined as the count at the time when the growth rate falls to a low value and the culture enters the stationary phase.

Experimental.—The medium consisted in an aqueous solution of glucose (35.7 g./l.), potassium dihydrogen phosphate buffer (3.21 g./l.) with enough sodium hydroxide to bring the pH to 7.12, ammonium sulphate (0.89 g./l.), magnesium sulphate (3.57×10^{-2} g./l.), together with the

¹ Lodge and Hinshelwood, *J.C.S.*, 1943, 213.

desired amount of disinfectant. The water used was distilled from the laboratory supply of distilled water through a silica condenser. Media, contained in sterile pyrex culture tubes suspended in a water thermostat at 40.0° , were aerated with a slow stream of washed sterile air. They were inoculated, sampled and counted by methods described previously.* The bacteria were stored in a meat extract medium and all inocula for the experiments to be described were derived from this after two passages through the aerated medium with no added disinfectant.

A. Resorcinol.

Lag.—The results are given in Fig. I. They show that (i) small concentrations of resorcinol reduce early and late lags slightly, (ii) at higher concentrations the lag increases rapidly, and (iii) the limiting resorcinol concentration, above which lag becomes infinite, depends upon the age of the inoculant.

Reduction of early and late lags implies that resorcinol either reacts with one of the constituents of the medium to give a substance capable of shortening the lag, or that it inhibits the action of some substance which lengthens lag and which is present as unavoidable impurity in the materials of which the medium is composed.

FIG. I.

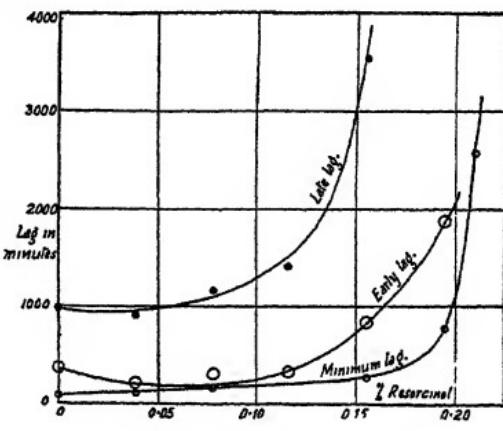


TABLE I.—THE EFFECT OF RESORCINOL ON STATIONARY POPULATION.

Resorcinol Concn., %.	Average Value of Stationary Population	Number of Determinations.
0.000	1972	3
0.020	1514	1
0.039	1176	12
0.058	1202	1
0.078	1193	11
0.097	1479	1
0.116	1039	4
0.155	1093	3
0.195	789	3
0.210	750	1

forms a compound with glucose * in the presence of the buffer.

Stationary Population.—The stationary population is independent of resorcinol concentration within the range which permits growth (Table I). This indicates that resorcinol is destroyed or titrated by the bacteria during

* Dagley and Hinshelwood, *J.C.S.*, 1938, 1930.

* Cf. Snell and Snell, *Colorimetric Methods of Analysis (Organic and Biological)*, 1937, p. 470.

The former hypothesis is supported by the observation that a yellow fluorescence develops when sterile media containing resorcinol are aerated at 40° for several days. The fluorescence depends for its formation on the presence of both glucose and phosphate, suggesting that resorcinol

growth. By the time the stationary phase is reached, no resorcinol is left in the medium, and the final population is limited by other factors.⁸

Growth Rate.—Fig. 2 shows the variation in growth rate with resorcinol concentration for inocula of different ages. It will be seen that,

when the inoculum is such that lag in the fresh medium is at a minimum, the growth rate is independent of resorcinol concentration up to about 0.08 %. Above this, the growth rate falls linearly with increasing resorcinol concentration. This type of behaviour is not given by either older or younger inocula. In these cases, as the resorcinol concentration is increased, the growth rate falls at first, then rises to about its original value, finally falling linearly as before.

The constancy of stationary population suggests destruction or inactivation of the resorcinol. The way in which the growth rate varies with resorcinol concentration may be explained on the same basis. With both

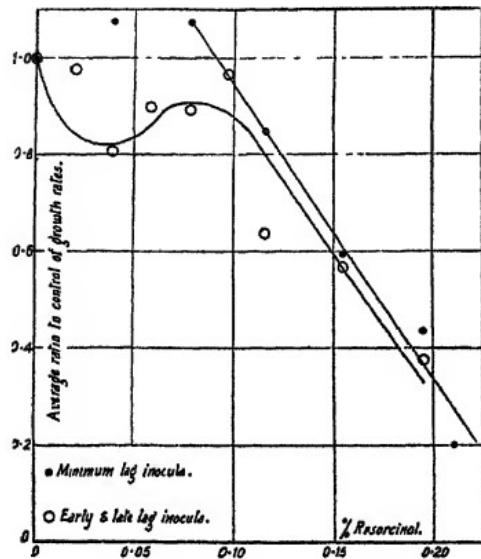


FIG. 2.

very young or very old inocula, the growth rate is less at 0.04 % resorcinol than it is at 0.08 %. However, at the higher resorcinol concentration the lag is longer (Fig. 1); accordingly, at the higher concentration, more time is available for the resorcinol to be destroyed by the bacteria, and, at the start of growth, the effective resorcinol concentration is greater in a medium initially containing 0.04 % resorcinol than in one containing 0.08 %. At concentrations greater than about 0.08 %, more resorcinol is present than the bacteria can neutralise during the lag phase, and the growth rate falls with increasing disinfectant concentration in the usual way.

Curves obtained by plotting the logarithms of the total bacterial counts against time are normally straight lines, the population, n , increasing with time, t , approximately according to the equation $n = n_0 e^{kt(L-t)}$, where n_0 is the initial number of bacteria, L the length of the lag phase, and k the growth rate constant ($= \log_e 2/m.g.t.$). Resorcinol cultures derived from inocula at the stage of minimum lag conform closely to this, but when younger or older inocula are used, the initial stages of such growth curves

TABLE II.—THE EFFECT OF THE AGE OF AN INOCULANT FREE FROM DISINFECTANT ON THE GROWTH RATE IN A MEDIUM CONTAINING 0.078 % RESORCINOL.

Age of the Inoculant, Minutes.	Growth Rate, $k \times 10^3$
253	1.63
372	1.66
434	2.00
491	1.89
583	2.14
677	1.89
2204	1.82

⁸ E.g. Graham-Smith, *J. Hyg.*, 1920, 19, 139; Lodge and Hinshelwood, *J.C.S.*, 1939, 1683.

are usually concave to the long n axis. The value of k increases as growth proceeds, indicating that the effective resorcinol concentration is falling during this time. Inocula taken from cultures at the minimum lag stage themselves appear to be able to destroy considerable amounts of resorcinol. Furthermore, there is in these cases a definite initial tolerance to resorcinol with respect to both lag and growth rate.⁴ It appears, therefore, that the bacteria synthesise some substance capable of neutralising the effects of resorcinol, and that this substance is present in greatest amount at the stage of minimum lag.

To investigate this further, the variation in bacterial growth rate in the presence of 0.0775 % resorcinol with the age of a resorcinol-free inoculant has been determined. The results, given in Table II, confirm that the concentration of the resorcinol inhibitor passes through a maximum at a time corresponding roughly to the stage of minimum lag.

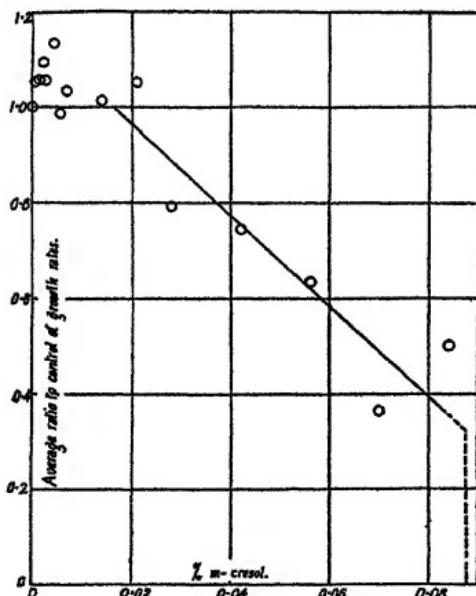


FIG. 4.

lags by small concentrations of disinfectant is observed. The highest concentration at which growth can occur is 0.084 % *m*-cresol with inocula

⁴ Cf. Poole and Hinshelwood, *J.C.S.*, 1940, 1565.

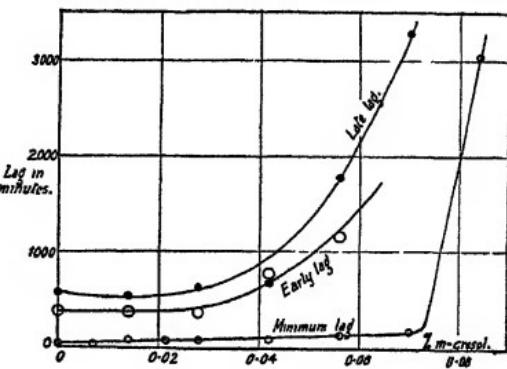


FIG. 3.

The inhibitor may be intracellular or it may be excreted by the bacteria into the medium. In the latter case, the addition of filtrate from a culture in the stage of minimum lag to media inoculated from a similar culture should increase the tolerance range of the bacteria to resorcinol. No such effect could be observed, and it may be concluded that the substance remains in the cells.

B. *m*-Cresol.

Lag.—The effects of *m*-cresol on the lag of *Bact. lactis aerogenes* in the artificial medium are generally similar to those produced by resorcinol (Fig. 3). A similar reduction of early and late

taken at the stage of minimum lag. With early and late lag inocula the limit is about 0·06 %.

Growth Rate.—There is an appreciable initial tolerance up to a limit at 0·02 % *m*-cresol. Increase of concentration above this value leads to a linear decrease in growth rate (Fig. 4). Very small amounts of *m*-cresol appear to cause a slight increase in growth rate.⁵ This is shown not to be due to the bacteria utilising *m*-cresol as a source of carbon more readily than glucose, since no growth could be detected in media free from glucose, but containing small amounts of *m*-cresol. The *m*-cresol may possibly react with some constituent of the medium so as to bring the latter into a more readily available form.

Stationary Population.—Table III. shows that there is a slight fall in the stationary population as the concentration of *m*-cresol is increased. This fact, together with the tolerance of the organism to *m*-cresol with respect to growth rate, indicates that the disinfectant is partially neutralised during the growth of the bacteria. This corresponds to type 3a of the growth rate-disinfectant concentration curves classified by Poole and Hinshelwood.⁶

TABLE III.—THE EFFECT OF *m*-CRESOL ON STATIONARY POPULATION.

<i>m</i> -Cresol Concn., %.	Average Stationary Population.	Number of Determinations.
0·000	1262	5
0·0007	966	1
0·0014	1175	1
0·0021	1862	1
0·0028	1585	1
0·0042	1084	1
0·0056	2042	1
0·0070	1334	2
0·014	918	3
0·021	785	1
0·028	918	3
0·042	811	3
0·056	547	3
0·070	546	4
0·084	661	1

the increase to infinity of the lag limits growth under these conditions. Similarly, the limiting concentration of resorcinol is that at which the lag is tending to become infinite, whereas, in the case of phenol⁴ the controlling factor is the reduction of the growth rate to zero.

Morphological Changes Induced by *m*-Cresol.—When the particular strain of *Bact. lactis aerogenes* used in this work is grown in media containing 0·07 % *m*-cresol, it undergoes a striking morphological change when the conditions are suitably adjusted. The bacteria, instead of appearing as the normal rod-shaped cells of length about 1 μ , undergo elongation along one axis to give thread-like cells. Single cells up to many hundreds of times the normal length are formed, and they may grow to lengths as great as 0·25 mm.

The production of filaments has been observed with *Bact. typhosum* when grown in the presence of methyl violet,⁸ with *Streptococcus viridans* in the presence of sulphanilamide,⁷ and with *Clostridium welchii*, the cholera vibrio and numerous other organisms in the presence of concentrations of penicillin insufficient to inhibit growth completely.⁸

⁵ Cf. Salter, *J. Inf. Dis.*, 1919, 24, 260.

⁶ Ainley Walker and Murray, *Brit. Med. J.*, 1904, 2, 16.

⁷ Tumnicliff, *J. Inf. Dis.*, 1939, 64, 59.

⁸ Gardner, *Nature*, 1940, 146, 837.

At the highest concentration at which growth can be observed (0·08 %), the stationary population is about 500; this is to be compared with 1500 for a culture containing no disinfectant. In this case, therefore, factors other than the reduction to zero of the stationary population preclude growth at higher disinfectant concentrations. Near the limiting *m*-cresol concentration, the lag is increasing very rapidly, but the growth rate is only falling slowly. It is clear that

Similar morphological changes occurred when the organisms were cultured in media in which the glucose concentration had been reduced to a twentieth of its normal value.* Here, the distribution of sizes of the cells was governed by the relation $n_l = ne^{-l/\bar{l}}$, where n_l is the number of cells with lengths greater than l , and \bar{l} is the mean length of all the cells of total number n .

To explain the phenomena occurring in dilute glucose media, it was suggested that the bacteria synthesise an intracellular substance (D) which influences their division. Evidence was adduced that another substance (L), synthesised and excreted by the bacteria, must be present in concentrations greater than a critical value before growth of bacterial substance, as distinct from division, can occur. In a similar way, it was assumed that (D) must be present in more than a critical concentration before division can occur. Filaments are formed when elongation proceeds normally while the probability of division is low, e.g., when the concentration of (D) is below the critical.

In media containing 0.07% *m*-cresol, the value of \bar{l} is very much greater than in the dilute glucose media. The actual number of cells is proportionately smaller, and a statistical study of sizes becomes more difficult. Fewer bacteria are in the field of view of the microscope at any one time, and the sizes of the very long cells are difficult to assess, since they tend to become tangled.

Since the filaments are very much longer in cultures containing *m*-cresol under the conditions described below, it appears that (D) is in very short supply, and that its synthesis is slowed down by *m*-cresol.

Conditions for the Formation of Snake-like Cells by *m*-Cresol.

We may now examine the conditions under which filaments are produced in the presence of *m*-cresol, and how each case may be explained by the above working hypothesis.

If a standard culture is subcultured at the minimum lag stage into a medium containing 0.07% *m*-cresol, filaments are produced after growth in the new medium has proceeded for some time. The filaments usually tend to disappear in the later stages of the culture cycle. The rate of synthesis of (D) is thought to be cut down by *m*-cresol, so that, as growth in the new medium proceeds, the concentration of (D) in the cells is not maintained at its original level in the inoculum; when it falls below the critical value the cells elongate but do not divide.

Minimum lag inocula containing 0.07% *m*-cresol give enhanced filament production when subcultured in the presence of 0.07% *m*-cresol. In this case the inoculum itself contains snake-like forms, and may be supposed to be lacking in (D). Growth in the presence of *m*-cresol therefore starts under conditions favourable for the production of filaments. Hence,

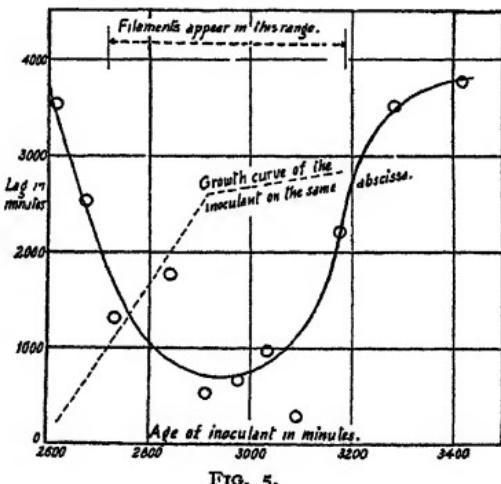


FIG. 5.

* Hinshelwood and Lodge, 1943, P.R.S., B, in the press.

elongation proceeds for a longer time than in the former case, and increased production of snake-like forms results.

If, instead of subculturing into media containing *m*-cresol, inocula similar to the above are grown in the standard medium free from disinfectant, no snake-like forms appear. Under these conditions, the rate of synthesis of (D) is always great enough for it to be provided in adequate amounts. As before, the inoculum from the culture containing *m*-cresol is deficient in (D). Even though lag is at its minimum, it is long enough for the deficiency to be made good before growth starts. The bacteria then divide as soon as other conditions become favourable, and the culture accordingly shows a normal appearance. The same reasoning applies to inocula taken at the late lag stage from media containing no *m*-cresol.

Inocula taken from cultures with or without 0·07 % *m*-cresol at the late lag stage do not produce filaments in media containing 0·07 % *m*-cresol. It appears, therefore, that the lag is long enough for the bacteria to build up a concentration of (D) so great that it is maintained above its critical value throughout the period of elongation. The reserve so formed is sufficiently great even though the synthesis of (D) is slow.

After the organisms have been subcultured ten times into media containing *m*-cresol, no diminution in the production of filaments is evident

provided that all inocula are taken at the minimum lag stage. Thus, no adaptation of the bacteria to the disinfectant occurs.

When a culture containing 0·07 % *m*-cresol is put into media containing the same concentration of disinfectant, the lag falls to a minimum at the onset of the stationary phase of the inoculant,¹⁰ and rises as the stationary phase proceeds (Fig. 5); filament production tends to a maximum when lag is shortest, no snake-like forms being given by either very young or very old inocula. With such inocula a sufficient reserve of (D) is built up before growth begins, so that it is not exhausted while elongation is in progress. When the

lag is short enough, there is a lack of (D) at some point in the growth cycle and filaments are produced.

If a culture containing 0·07 % *m*-cresol is put back into the medium free from disinfectant at the onset of the stationary phase, the growth rate of the subculture has a normal value. As the inoculant ages further, the growth rate falls to a minimum and filaments appear only in those subcultures which grow slowly. Maximum production of snake-like cells coincides with slowest growth. As the inoculant ages still further, the growth rates of the subcultures gradually revert to normal and the production of filaments ceases simultaneously (Table IV). If the slow-growing organisms are repeatedly subcultured in media containing no *m*-cresol, their growth rates gradually increase and the tendency to give filaments gradually disappears. Almost complete recovery is brought about by forty such subcultures, but it is evident that the cells must have suffered some profound change for recovery to take so long. This change is further evidenced by the variation in growth rate with the age of the inoculant culture, described above.

To explain these phenomena it is suggested that, during the stationary phase as the inoculant containing *m*-cresol ages, a point is reached at which

¹⁰ Cf. Lodge and Hinshelwood, J.C.S., 1943, 213.

the permeability of the cell walls to *m*-cresol falls abruptly and almost to zero. It must also be assumed that the *m*-cresol present in the cells modifies both those parts of the bacteria responsible for synthesis of (D) and those which control the growth of bacterial substance, and that the change takes a considerable time to occur. The modification in fact occurs mainly during the lag phase between inoculation and the start of growth in the medium free from *m*-cresol.

Thus, when a culture containing 0.07 % *m*-cresol is subcultured in the early part of the stationary phase, the lag is short and there is little time for any damage to occur. Hence, normal growth ensues. With older inocula, the lags of the subcultures become longer and there is more time for the *m*-cresol to act. Hence, growth is slow and filaments are formed. Finally, however, the state is reached when the *m*-cresol can no longer penetrate the cell walls, and that which is already inside the cells must become neutralised by oxidation or other means. Upon subculture at this stage, therefore, the cells suffer no damage and growth is again normal.

It is a pleasure to record our gratitude to Professor Hinshelwood for his help in connection with this work.

Summary.

The influences of resorcinol and of *m*-cresol on lags, growth rates and stationary populations of *Bact. lactis aerogenes* in liquid artificial media have been studied.

The ways in which these characteristics of growth are changed by various concentrations of disinfectant lead to the following conclusions.

(1) Both disinfectants have specific actions on various stages of cellular metabolism in different ways.

(2) Indefinite prolongation of the lag rather than reduction of the growth rate or of the stationary population to zero causes inhibition of growth at the higher disinfectant concentrations.

(3) The effects of resorcinol can be completely neutralised by the bacteria during growth; with *m*-cresol, on the other hand, only partial neutralisation occurs.

At a certain concentration of *m*-cresol, and with carefully controlled inocula, the bacteria undergo a morphological change and grow to thread-like cells many times their normal length. The theory that elongation and division are processes controlled by separate factors is applied to the experimental results.

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THE ADAPTATION OF BACT. LACTIS AEROGENES TO GROWTH IN THE PRESENCE OF SULPHONAMIDES.

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The object of the work to be described was to study the action of sulphonamide compounds upon the growth of *Bact. lactis aerogenes*. Previous work with this organism showed that various antiseptic agents acted in specific ways upon different parts of the growth mechanism, some, for example, lengthening the lag phase, others reducing the actual rate of

multiplication progressively to zero.¹ The action of the typical sulphonamides chosen proves to be unlike that of most other antiseptic agents: it is never complete, and it provokes responses whereby the bacteria become immune to the drug. The immunisation—well known in the clinical literature—is itself of some complexity. Some of the threads of these matters have now been disentangled. The results may be of some indirect medical interest, but we shall be primarily concerned with the help they may give towards constructing a physico-chemical theory of cell growth and adaptation.

Method.—The strain of *Bact. lactis aerogenes* used had been maintained since 1937 by monthly subculture in bouillon. Minor changes in growth rate were observed between 1937 and 1942, but experiments in 1942 showed that the strain was still homogeneous.

An artificial medium was used in all experiments. It contained: 10 cc. of glucose 100 g./l.; 10 cc. KH_2PO_4 , 9 g./l., ρH adjusted to 7.2 with NaOH; 5 cc. of either a 5 g./l. solution of ammonium sulphate or of a 5 g./l. solution of asparagine; 1 cc. magnesium sulphate, 1 g./l. Solutions were made up in twice distilled sterile water and sterilised by intermittent boiling.

The sulphonamides in aqueous solution were added as required, the additions not normally exceeding 2 cc. To obtain higher concentrations of sulphaguanidine (which is less soluble than sulphanilamide) portions of a solution saturated at 50° were added.

The inhibition of growth, known from the original work of Tréfouel and others,^{2, 3} was followed by examination of the complete growth curves, which were determined as follows. A tube of the standard medium was inoculated with a loop or two of the bouillon culture and incubated at 39.7° in a gentle stream of sterile air. At a suitable stage in its growth this culture was used as inoculant for quantitative experiments. Inocula were transferred by means of a 0.1 cc. pipette: the initial populations varied from 10^6 to 10^7 cells per cc. When cloudiness began to develop, samples were withdrawn at suitable intervals, killed and stained immediately, and set aside for counting. Counts were determined in a haemocytometer with a chamber of depth 0.02 mm. The mean count, n , is given per unit square: the population per cc. is $1.25 \times 10^6 n$.

Characteristics of the Normal Growth of *Bact. lactis aerogenes* in the Standard Medium.—In normal growth there is a well-defined logarithmic phase, where $n = n_0 \exp.(kt)$. This usually continues to $n = 800$, when growth slows up sharply, but continues for some time till the stationary population (n_s) is attained. This is usually about 2000. The most convenient measure of growth is the mean generation time (m.g.t.), i.e. the time required for the number of cells to double. Before the proliferation of the cells starts there is the usual lag phase, measured by extrapolating the logarithmic growth curve back to $n = n_0$. A typical curve is shown in Fig. 1. The lag depends upon the age of the inoculum: if the latter is very young, the lag is considerable, and has been called "early lag." As the cells of the inoculum age, the lag falls nearly to zero and then increases again. It is convenient to refer to cultures in the "early lag," "zero lag," or "late lag" state. The early lag is the time required to build up a critical concentration of a growth promoter which diffuses from the cells into the medium.^{4, 5} In the late lag state various enzyme systems have lost their activity.

¹ Poole and Hinshelwood, *J. Chem. Soc.*, 1940, 1565.

² Tréfouel, J., Tréfouel, Mme. J., Nitti and Boret, *Compt. Rend. Soc. Biol.*, 1936, 120, 756.

³ Tréfouel, J., Tréfouel, Mme. J., Nitti, Boret and Fourneau, 1937, *ibid.*, 122, 258.

⁴ Lodge and Hinshelwood, *J. Chem. Soc.*, 1943, 213.

⁵ Hinshelwood and Lodge, 1943, *in the press*.

Form of the Growth Curve in Presence of Sulphonamides.—This is shown in Fig. 1. When *Bact. lactis acrogenes* is grown for the first time in a medium containing the sulphonamide, the logarithmic phase is composite: the growth curve consists of two parts with an intersection at what we shall term the "transition point." Here growth with a longer m.g.t., which we shall call m.g.t. I, is superseded by growth with a shorter m.g.t. which will be called m.g.t. II.

M.g.t. I and m.g.t. II as Functions of Sulphonamide Concentration.—The retarding effect of the drug on logarithmic growth is best expressed by recording the ratio of the m.g.t. for normal growth to the observed value in presence of the sulphonamide. M.g.t. I and m.g.t. II both increase as the concentration increases (Fig. 2), i.e. the ratios, which measure the relative rates of growth, fall.

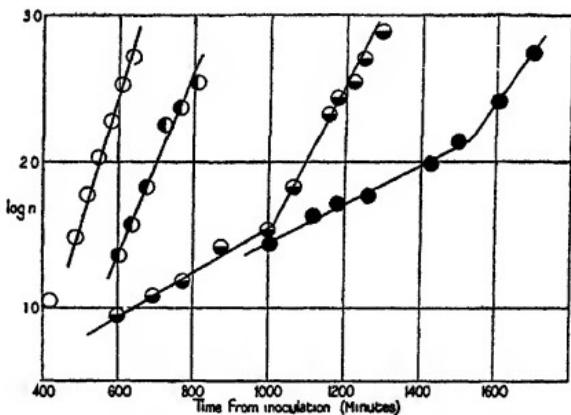


FIG. 1.—Typical Growth Curves. Open circles, normal culture; vertically divided circles, growth with 4.56 p.p.m. million sulphamamide; horizontally divided circles—30.6 p.p.m. sulphamamide (times plotted = actual times—600); full circles—46.7 p.p.m. sulphamamide (actual times—1200).

The results do not, however, fall to zero (as would, for example, be found with phenol), but to well-defined limits as seen in the figure.

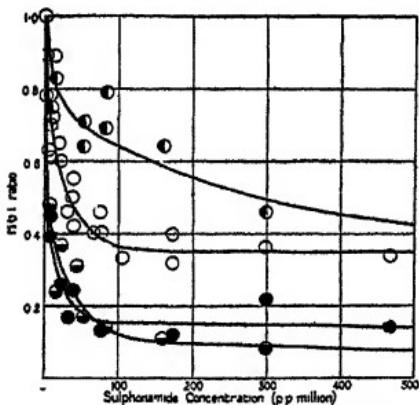


FIG. 2.—Influence of Drug Concentration on m.g.t. Ratio. Full circles—m.g.t. I in sulphonamide (SA). Open circles—m.g.t. II in SA. Horizontally divided circles—m.g.t. I in sulphaguanidine (SG). Vertically divided circles—m.g.t. II in SG.

Early and Late Lag as Functions of the Sulphonamide Concentration.—The lags all increase with the sulphonamide concentration: the results are given in Table I. The values for the early lags must be regarded as approximate only, since the extrapolation of the lower segment of the growth curve was uncertain with the small inocula used in early lag determinations, and an indirect method was used. The results, however, show that the lags increase steadily with increasing concentration, and show much less tendency to

reach a limit than the mean generation times. Lag and m.g.t. are, in fact, separate and individual functions of the sulphonamide concentration.

Interpretation of the Transition Point.—This might have been interpreted as the point at which the cells have excreted enough of some

product which neutralises the action of the sulphonamide, or, in view of possible effects of pH on sulphonamide action,⁶ as a point at which rapid change of pH occurs. Neither explanation fits. According to the first, the transition point would probably move to higher counts the greater the amount of drug to be dealt with. Actually it varies as in Fig. 4. The second is disproved by direct observation on the pH , which falls to about

TABLE I.—EFFECT OF SULPHONAMIDES ON LAG.

Sulphanilamide Concentration (parts/million).	Late Lag (minutes).	Early Lag (minutes).	Sulphaguanidine Concentration (parts/million).	Late Lag (minutes).
<i>Series I.</i>				
0	925		0	1575
2.2	971		15.1	2034
4.4	1041		29.1	2291
6.5	1102		42.1	2678
20.2	1375		82.5	3316
39.7	1474		160	4958
			298	Did not grow
<i>Series II.</i>				
0	863	340		
20.2	2197	830		
39.7	2736	660		
107	2924	620		
299	3555	2674		
467	4798			

6.0 during the lag and, whether sulphonamide is present or not, remains nearly constant during most of the logarithmic phase.

The true explanation is suggested by the observation that subcultures taken toward the end of the second stage of the logarithmic phase show a much earlier transition point, and indeed may grow from the start with m.g.t. II. All the facts can be correlated by the following scheme. There are two modes of growth which may be referred to as I and II. I is the

normal mode, and is sensitive to the presence of the drug. II is an alternative mode, not normally called into play, because it is less rapid than I. Ordinarily the enzymes involved in II are not immediately utilisable, but are in a state corresponding to the late lag phase. When mode I is largely put out of action by the sulphonamide, mode II, which is less sensitive to the drug, can compete on more equal terms.

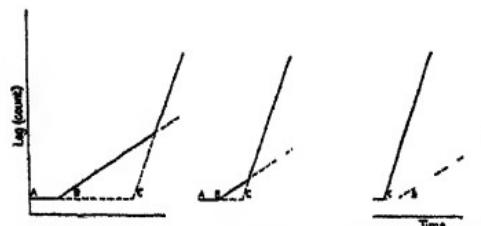


FIG. 3.—Adaptation by the Progressive Shortening of the Lag of a Reserve Mechanism. AB = lag of normal (but retarded) mechanism. AC = lag of reserve mechanism.

terms. We have, therefore, a superposition of mode I with shorter lag and slower growth rate, and mode II with longer lag and more rapid growth. This is shown in Fig. 3, where the transition point is given by the intersection of the two growth curves. On subculturing cells which have once been grown in presence of the drug, the lag of mechanism II is shortened,

* Rose and Fox, Proc. Soc. Exp. Biol. Med., 1942, 50, 142.

with lowering of the transition point, as shown, or even complete replacement of mode I by mode II.

This view of the matter is confirmed by three sets of observations:—

(1) The lag in a medium containing sulphonamide is, in fact, less for cultures which have already been grown in presence of the drug (Table VII).

(2) The "immunity" of the subculture decays as the inoculum ages (Table VI). This is due to the normal development of lag with age. Ordinarily the lag of mode II is greater than that of mode I: when mode II has been mobilised by growth in sulphonamide its lag is shortened relatively to that of mode I, but on ageing of the cells there is reversion to the normal relationship.

(3) The curve of transition point against drug concentration is very different for sulphanilamide and for sulphaguanidine. This can be simply explained. Let the two modes of growth have lags L_1 and L_2 and growth constants k_1 and k_2 respectively, then

TABLE II.—EFFECT OF SULPHANILAMIDE ON STATIONARY POPULATION.

Sulphanilamide Concentration (Parts/million).	n_s
0	920
2.2	1440
2.85	1140
4.4	1300
5.5	1600
6.5	1760
10.7	1620
20.2	2340
39.7	3240
54.6	3540
107	2260
299	2760
467	1600
	1330
	730
	780

$$n_1 = n_0 e^{k_1(t - L_1)} \quad \text{and} \quad n_2 = n_0 e^{k_2(t - L_2)}$$

The transition point occurs where $n_1 = n_2 = n_t$, so that

$$L_2 - L_1 = 2.303 \log \frac{n_t}{n_0} \left\{ \frac{1}{k_1} - \frac{1}{k_2} \right\}.$$

From the dependence of n_t on concentration in Fig. 4b, using the known dependence of k_1 and k_2 on concentration (Fig. 2), the variation of $L_2 - L_1$ has been calculated and plotted in Fig. 4a. The apparently quite different curves in Fig. 4b can be explained, as shown, by the relatively small quantitative differences in the effects of the two drugs on $(L_2 - L_1)$, which are not such as to cause surprise.

Stationary Population.—The variation of n_s with sulphonamide concentration is given in Table II. The final pH of sulphonamide cultures is higher than normal, which may in part explain the occurrence of a maximum.⁷

Growth in Presence of Sulphonamides of Cultures in the "Zero Lag" State.—This is anomalous, and can be explained by assuming that the sulphonamide requires time to exert its effect—either because it is slow in penetrating into the cell, or because it must suffer a preliminary chemical change.⁸ Growth begins

⁷ Lodge and Hinshelwood, *J. Chem. Soc.*, 1939, 1683.

⁸ Main, Shinn, and Millon, *Proc. Soc. Exp. Biol. Med.*, 1938, 39, 272, 591; 1939, 42, 115; 1940, 43, 593.

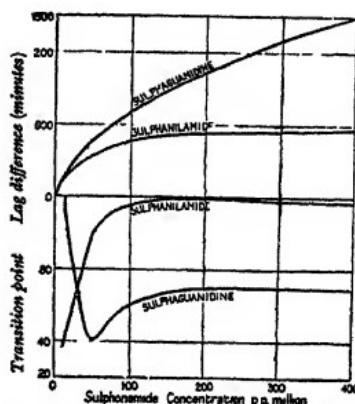


FIG. 4.—Lower Curves: Actual Variation of Transition Point with Drug Concentration. Upper Curves: Inferred Change of Lag Difference with Drug Concentration.

rapidly, at nearly the rate in the standard medium, but at an early stage it suffers an arrest, greater at high sulphonamide concentrations, after which the phenomena are as previously described. Fig. 5 shows some typical curves.

As the lag of the inoculant lengthens, the arrest becomes more marked and finally the initial phase of rapid growth disappears.

Influence of Aminobenzoic Acid and of Filtered Medium from Old Cultures.—Aminobenzoic acid is known to antagonise the action of sulphonamides.* To determine whether it would produce a change similar to the transition from growth with m.g.t. I to that with m.g.t. II, the measurements in Table III were made. The aminobenzoic acid is found to restore the growth rate to normal, i.e. to reduce the m.g.t.

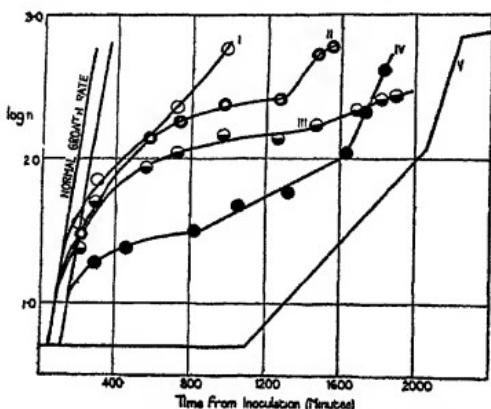


FIG. 5.—Initial Rapid Growth of Cultures with Short Lag. I. 107 p.p.m. SA, minimum lag. II. 299 p.p.m. SA, minimum lag. III. 467 p.p.m. SA, minimum lag. IV. 107 p.p.m. SA, lag 114 minutes. V. 299 p.p.m. SA, late lag.

I to well below m.g.t. II. What we have called mode II of growth, therefore, seems not to be associated with excess aminobenzoic acid production.

TABLE III.—EFFECT OF ADDITION OF FOREIGN SUBSTANCES TO SULPHANILAMIDE CULTURES.

Sulphanilamide concentration in parts/million = c.

(i) Sulphanilamide alone.

c = .	0	10·7	39·7	107	299
m.g.t. I.	35'	88'	165'	220'	220'
m.g.t. II.		52·8'	68·9'	90·4'	97'
lag (early)	340 increasing to 1300 mins.				
n _s . .	1300	3500	1500		

(ii) Sulphanilamide with 7·6 p.p.m. p-aminobenzoic acid.

c = .	0	10·7	39·7	107	299
m.g.t. .	36'	31·6'	32·6'	34'	ca. 40'
lag .	330	231	213	113	ca. 80 mins.
n _s . .	1480	1460	1600		

(iii) Sulphanilamide with 1/13 parts by vol. of centrifuged filtrate.

c = .	0	10·7	39·7		
m.g.t. I.	36'	—	140'		
m.g.t. II.	—	45·4'	79·2'		
lag .	27'	meaningless			
n _s . .	1140	2390	1700		

Since the medium removed by filtration or centrifuging from a culture in the zero lag state has a very marked effect in reducing the early lag of

* Woods, Brit. J. Expt. Path., 1940, 21, 74.

inocula in the standard medium,⁴ it was thought of interest to determine what effect this filtrate would have on sulphonamide action. The usual reduction of lag is observed, but no neutralisation of the other actions of the drug (Table III).

Growth in an Asparagine Medium.—When the ammonium sulphate in the standard medium is replaced by asparagine, the effects of the sulphonamide remain qualitatively the same, but the relative values of the m.g.t.'s are changed. M.g.t. I in the asparagine medium is uniformly higher, i.e. the growth mechanism which utilises the amino acid is more sensitive to the action of the drug. On the other hand, m.g.t. II, that of the reserve mechanism, is the same for both media (Table IV). The adaptation

TABLE IV.—GROWTH IN PRESENCE OF SULPHANILAMIDE WITH ALTERNATIVE NITROGEN SOURCES.

Nitrogen Source.	Sulphanilamide Concentration (parts/million).	Lag (mins.).	m.g.t. I. (mins.).	m.g.t. II. (mins.).
Ammonium Sulphate .	117	2000	194	76
	225	4075	220	57
Asparagine .	117	2275	386	90
	225	1500	1545	60

phenomena described below occur in the same way whichever nitrogen source is used, either for training or for testing.

Adaptation of Bact. lactis aerogenes to Growth in Presence of Sulphonamides: Training Phenomena.—The immunity towards sulphonamides developed by the cells after growth in their presence has already been referred to. The development of this immunity has been studied in some detail. For the quantitative measure of it we define a "training coefficient" as follows: let t be the time required for the count of the culture to increase from 20 to 200, then

$$T = \frac{t_{\text{trained}} - t_{\text{untrained}}}{t_{\text{untrained}} - t_{\text{trained}}}.$$

The progress of training may, according to circumstances, be reflected in a shift of the transition point to lower values of n , or in a decrease in the value of m.g.t. II. Both increase T . An untrained culture has $T = 0$, one for which the transition point has been so far lowered that all growth occurs with the m.g.t. II of the first growth in sulphanilamide has $T = 0.8$, while one so completely trained that it grows like a normal culture in absence of drug has $T = 1.0$.

Complete Adaptation.—After 23 or 30 subcultures in a medium containing 216 p.p. million sulphanilamide the characteristics of the final cultures were as follows: (1) T approached 1.0. (2) T did not decrease much as the culture aged. (3) The adaptation was non-specific: cultures trained in sulphanilamide showed a high degree of immunity to sulphaguanidine. (4) T did not show a rapid or serious decline after several passages through the standard medium containing no sulphonamide and subsequent test in presence of sulphanilamide. These facts are illustrated in Table V.

Development of Adaptation. First and Second Cultures in Sulphonamide Media.—The chief facts are shown in Figs. 6 and 7. After one passage through sulphanilamide the cells are well enough trained to grow in a second culture at m.g.t. II throughout. This training is specific: when identical inocula from a sulphanilamide culture are transferred to media containing sulphanilamide and sulphaguanidine respectively, they

are trained towards the former but not towards the latter, and *vice versa* (Fig. 6). The training is shown both in the reduction of lag, and in the earlier transition point.

TABLE V.—GROWTH OF CELLS SUBCULTURED 30 TIMES IN PRESENCE OF SULPHANILAMIDE

(i) *Growth after passage through normal medium.*

No. of Passages (Total Time in Brackets).	in g.t. II. (mins.).	Training Coefficient T in SA 216 p.p.m.
0 (completely trained strain)	27.6	1.03
1 (29 hours) : : : .	44.4	0.73
2 (100 hours) : : : .	43	0.81
5 (15 days)	46	0.88
5 times in artificial medium as above, then 3½ weeks in bouillon . .	45.6	0.81
After 3½ weeks in bouillon and then 16 sub-cultures in normal medium .	43.6	0.80
Ditto and 17 sub-cultures in normal medium	41.4	0.76

(ii) *Variation of adaptation with age of inoculant.*

Time from Onset of Stationary Phase of Parent (mins.).	T in 225 p.p.m. Sulphamamide.	T in 160 p.p.m. Sulphaguanidine.
0	1.03	0.99
1090	0.87	0.85
2555	0.67	0.80
4040		0.84

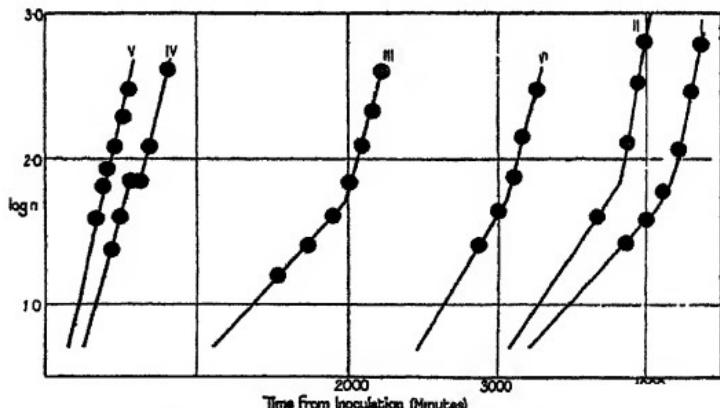


FIG. 6.—Early Stages of Adaptation to Sulphonamides. I. Untrained growth in SG (160 p.p.m.). II. Untrained growth in SA (218 p.p.m.). III. Culture in 160 p.p.m. SG. IV. Culture in 225 p.p.m. SA; III. and IV. both inoculated at same time from a parent culture in 225 p.p.m. SA. V. Culture in 160 p.p.m. SG. VI. Culture in 225 p.p.m. SA; V. and VI. both inoculated at same time from parent culture in 160 p.p.m. SG.

TABLE VI.—CHARACTERISTICS OF ADAPTATION AT SECOND SERIAL SUBCULTURE IN PRESENCE OF SULPHONAMIDE.

SA = sulphanilamide. SG = sulphaguanidine.

(a) Effect of variation in age of parent. Parent and test cultures contain 220 p.p.m. SA.

Age, measured from Onset of Stationary Phase. (mins.).	m.g.t. II (mins.).	T.
<i>Series I.</i>		
-460	67	0.13
0	74.6	0.58
807	82.0	0.35
<i>Series II.</i>		
0	88	0.25
2410	58.4	0.13
3890	96	0.02
4650	52	-0.04
6355	—	0.01

(b) Change of immunity to SA and SG with age of parent. Parent grown in 225 p.p.m. SA.

Age, measured from Onset of Stationary Phase. (mins.).	T in 225 p.p.m. SA.	T in 160 p.p.m. SG.
0	0.69	0.26
928	0.32	0.28
2246	0.2	-0.18

(c) Loss of immunity after passage through normal medium.

	Lat. (mins.).	m.g.t. I (mins.).	m.g.t. II (mins.).	T.
Parent (3rd culture in 220 p.p.m. SA)	30	—	62	0.70
Culture in 220 p.p.m. SA after growth in normal medium	280	198	58.2	-0.14

(d) Effect of growth in one drug on immunity toward another.

Drug in Inoculent Culture.	Drug in Test Culture.	Lat. (mins.).	m.g.t. I (mins.).	m.g.t. II (mins.).	T.
220 p.p.m. SA	220 p.p.m. SA	250	—	78.0	0.33
220 p.p.m. SA	160 p.p.m. SG	1060	264.0	80.8	-0.12
160 p.p.m. SG	220 p.p.m. SA	2430	194.0	76.0	0.12
160 p.p.m. SG	160 p.p.m. SG	120	—	68.0	0.65

After one passage through the standard medium without sulphonamide the immunity is largely lost (Fig. 7). The immunity has not been attained until some time past the transition point, as shown by one of the curves in Fig. 7.

The immunity decays as the culture ages (Table VI).

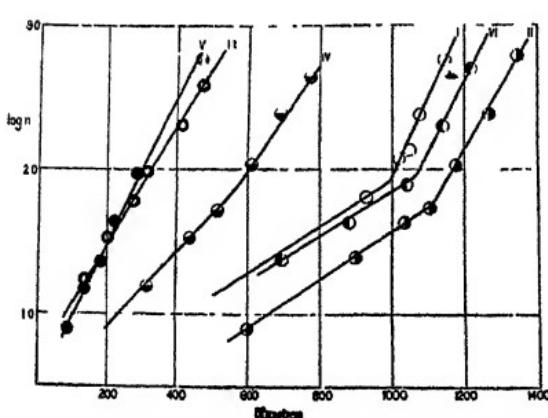


FIG. 7. Development and Decay of Adaptation in Early Stage. All cultures in 218 p.p.m. SA. I. First culture (time zero 2000 minutes from origin). II. Second culture in SA inoculated at transition point. III. Second subculture, inoculated at onset of stationary phase. IV. Second subculture, inoculated 800 minutes after onset of stationary phase. V. Strain made immune by three passages through SA, inoculated at onset of stationary phase. VI. Strain, from V as parent, whose adaptation has been lost after passage through normal medium.

The lag is in any case a function of the age of the inoculum, but for inocula of comparable ages the lag is much less in the second sulphanilamide culture than the first (Table VII).

Progressive Development of the Adaptation.—Repeated subcultures were made in the standard medium containing 225 p.p.m. sulphanilamide. At frequent intervals the following quantities were determined : (1) T in sulphanilamide, (2) T in sulphaguanidine, (3) T in sulphanilamide of the subculture which had been passed in the meantime through the standard medium containing no sulphonamide, (4) the value of m.g.t. II in the sulphanilamide medium. The results are shown in Fig. 8, which reveals the following facts. The specific immunity to one drug develops more rapidly than the non-specific immunity to both, though the final state is complete adaptation both to sulphanilamide and to sulphaguanidine. The irreversibility of the adaptation also develops according to its own characteristic curve.

For the earlier serial subcultures the increase in the value of T is due principally to the lowering of the transition point, m.g.t. II showing little change. In the later stages of the training process, m.g.t. II itself begins to decrease and ultimately falls nearly to the standard value for normal growth.

TABLE VII.—VARIATION OF LATE LAG WITH AGE OF PARENT IN SULPHANILAMIDE CULTURES.

The zero of the age scale is taken as the point at which the count of the parent is 1000.
All test cultures contained 225 p.p.m. of sulphanilamide.

Count of Inoculant.	Age (min.).	Lag (min.).
<i>(a) Normal culture as parent.</i>		
1400	310	100
1440	958	2410
—	1645	2140
1900	3020	3940
<i>(b) Culture grown in 225 p.p.m. sulphanilamide as parent.</i>		
1000	0	14
1300	910	265
1340	1508	1421
2080	2810	2060

Non-specific immunity of bacteria to sulphonamides after repeated subculture in their presence has been reported by Kirby and Rantz.¹⁰ Table VIII shows that adaptation can occur quite readily in presence of

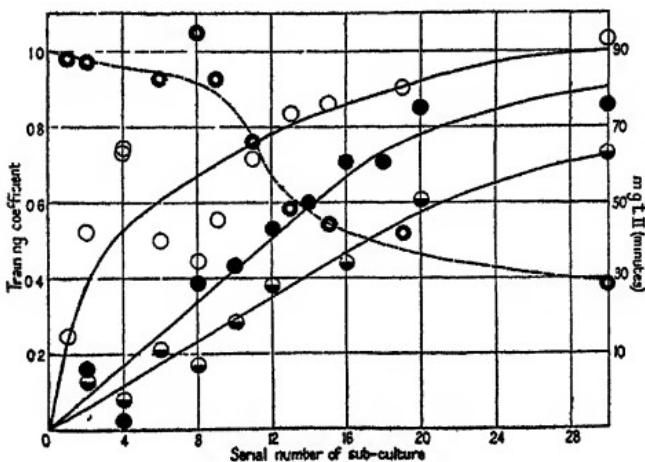


FIG. 8.—Progressive Development of Training in Presence of SA. Open circles, training coefficient, T , in SA. Full circles, T for SG. Horizontally divided circles, T in SA after passage through normal medium. Black rimmed circles, m.g.t. II in SA (ordinates on right of figure).

TABLE VIII.—GROWTH AND ADAPTATION IN MEDIA CONTAINING TWO SULPHONAMIDES.

Drug in Parent Culture.	Drug in Test Culture.	Lag (minutes).	m.g.t. I (minutes).	m.g.t. II (minutes).	T .
None . . .	{ 113 p.p.m. SA 80 p.p.m. SG }	2800	211.2	90.4	○
None . . .	160 p.p.m. SG	2200	unknown	45.2	○
225 p.p.m. SA	{ 113 p.p.m. SA 80 p.p.m. SG }	1700	235.2	71.2	0.2
225 p.p.m. SA	160 p.p.m. SG	1850	194.8	65.2	—0.48
	225 p.p.m. SA	35	—	53.0	0.6
113 p.p.m. SA 80 p.p.m. SG	{ 113 p.p.m. SA 80 p.p.m. SG }	25	—	64.6	0.67
	160 p.p.m. SG	40	—	49.4	0.54
					inoc. from same culture at same time.

a mixture of sulphanilamide and sulphaguanidine, i.e. there is nothing in the mechanism of one specific type of training which excludes the simultaneous occurrence of the other.

¹⁰ Kirby and Rantz, *J. Exp. Med.*, 1943, 77, 29.

Discussion.

(a) Formal Interpretation of Results.

(1) Since the final adaptation to the sulphonamide is complete, non-specific and difficultly reversible, and since various substances such as aminobenzoic acid or methionine¹¹ are known to antagonise the action of the drugs, the simplest hypothesis to make is that during training the cells develop the enzymes necessary for the synthesis of an appropriate sulphonamide antagonist. Once developed, these enzyme systems, for reasons which will be discussed below, are relatively permanent.

(2) In the earlier stages the adaptation is different: it is specific, easily reversible, not only by subculture in the normal medium, but by simple ageing of the cells, and manifests itself chiefly by a lowering of the transition point. As we have seen, it is interpretable as a shortening of the lag phase of a reserve growth mechanism. The mobilisation of this mechanism is, however, but a temporary expedient, which serves while the more radical solution is being developed.

(3) The initial adaptation being little more than the shortening of a lag, it is easy to understand why in the early stages of training the immunity is readily lost: the natural lengthening of lag, as cultures age, is a phenomenon of general occurrence.

(4) The complex effects of the sulphonamides upon growth suggest that the drugs do not so much interfere with a single link in the series of vital processes as bring about a general disorganisation of the cell. The response of the cell is correspondingly complex.

(5) The curves in Fig. 2 show that growth cannot be entirely inhibited. If we think of the enzymes responsible for the cell processes as constituted by protein patterns of various kinds, then we must conclude that there are certain groupings which are not affected by the drugs and which are capable of serving the needs of the cell, though less efficiently than those in normal use.

(6) The patterns which serve as the basis of enzyme functions may be almost infinitely varied. In the presence of sulphonamide, fresh configurations may be slowly built up which can perform the essential reactions of the cell in spite of the adverse conditions. This may well occur during the lag phase of the mechanism corresponding to m.g.t. II. Since the immunity which develops is specific to one drug, quite delicate structural or stereochemical relations seem to be involved at this stage.

It is important to note that the specificity is reciprocal in the early stages of immunisation, i.e. training in sulphaguanidine does not immunise to sulphanilamide, nor *vice versa*. (It might have been found that the drugs could be arranged in an order of potency, training in the presence of the more powerful members of a series immunising towards all the less powerful members.)

(b) Natural Selection and Adaptation.

Where repeated sub-culture changes the character of a bacterial population, two hypotheses are possible. First, we may assume the initial population to have been made up of several distinct strains, one of which increases relatively to the other during successive growth cycles. This we shall call selection, restricting the term to a mere shift in the numerical balance between non-interconvertible types. Secondly, we may suppose that in successive generations the cells of one initial type undergo modification of their enzyme systems. This we shall call adaptation.

In many respects the consequences of the two hypotheses are the same, but in interpreting the above results we prefer the latter for the following reasons: (1) In the early stages of training the adaptation is lost on

¹¹ Bliss and Long, *Bull. Johns Hopkins Hosp.*, 1941, 69, 14.

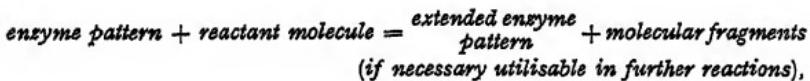
passage through the normal medium. This reversal, according to the selection hypothesis, would mean that the postulated sulphonamide-resistant strain actually grew less well in the normal medium: an assumption which is not impossible, but unlikely. (2) Immunity decreases with the age of the culture. This would mean that the type which grew most readily in presence of sulphonamide also died off most rapidly: again, a very unlikely conclusion. (3) The training is a multiple process, different functions adapting themselves at different rates, as shown by Fig. 8. In terms of the selection theory this would mean that there were present initially, not two but a whole spectrum of bacterial strains. Since the culture used was originally derived from a single colony, this could only be true if one original type had at one stage become heterogeneous—an assumption which itself admits the possibility of continuous modification of the strain. It is therefore simpler and more logical to explain the observed changes by assuming an actual adaptation of the enzyme systems.

(c) Nature of the Adaptation Process.

(1) We regard adaptation as a modification of the enzyme balance of the cell.

(2) In particular, when a certain function of the cell develops during the adaptation process, we imagine that there occurs an expansion of certain protein patterns.

(3) We now ask why this expansion occurs in response to a need of the cell. We believe the answer to be that it will, in fact, occur automatically when some key process can be formulated according to the general scheme:



the enzyme expanding as it does its work. Its amount will then increase with time according to the law $x = x_0 e^{kt}$ during certain periods.

(4) An example of adaptation reduced to its simplest terms may now be considered. Let there be two enzyme systems present in the cell, the first in very small amount x_0 , and the second in large amount y_0 . Let both operate according to the above scheme. Consider growth in a medium in which x_0 increases at a small rate k_x while y_0 increases at a greater rate k_y . The cell divides when it reaches a certain size, at which time y_0 will have expanded to some amount y_1 while x_0 will only have increased to x_1 , where

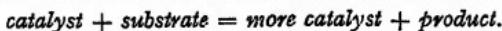
$$\frac{x_1}{y_1} = \frac{x_0 e^{(k_x - k_y)t}}{y_0}$$

Now let the cell be transferred to a medium where the essential reactants for the increase of "y" are in short supply, so that the specific rate k_y is reduced to k'_y . The cell now makes more use of the products of the x-enzyme. Let division still occur when y_1 is reached: the value of x_1 at this point is now given by $\frac{x'_1}{y_1} = \frac{x_0 e^{(k_x - k'_y)t}}{y_0}$, so that $\frac{x'_1}{x_1} = e^{(k_y - k'_y)t}$. Thus the new cell starts with a better supply of enzyme "x" than did its parent. When it, in turn, divides, we have $\frac{x''_1}{x'_1} = e^{(k_y - k'_y)t}$, and so on, until enzyme "x" takes control and the moment of division depends upon the attainment of a given value of x_1 . If the two enzymes are independent, and concerned in alternative, rather than in linked mechanisms, their amounts cannot stand in a fixed relation during cell growth, unless the two rate constants are identical, which would not in general be true.

Naturally in real examples the adaptation would be a complicated combination of schemes of which the above is a crude illustration only.

GENERAL DISCUSSION

(5) The fundamental scheme in paragraph (3) of this section has simple analogies in other parts of chemistry. The decomposition of arsine is catalysed by a surface of metallic arsenic, so that we have:



This scheme can be extended to any case where an ordered structure expands by the accretion of new units. The order thereby created represents a decrease in free energy which can compensate accompanying increases, in the formation of other reactive products. Certain protein patterns may well extend themselves by removing suitable fragments from other molecules, leaving residues which can participate in other cell reactions. If this type of coupling lies at the basis of the equation in paragraph (3), then adaptation can be understood in principle.

(6) From the above, it seems that an enzyme system will remain in use only when it is the most efficient means available for a particular purpose. To explain the persistency, during growth in the normal medium, of the antagonist-forming mechanism invoked to explain adaptation to the sulphonamide (see above), we must assume that this process can also be used with advantage in normal growth. Such a circumstance is by no means unlikely.

Summary.

The influence of two typical sulphonamide compounds (sulphanilamide and sulphaguanidine) on the growth of *Bact. lactis aerogenes* has been studied. Increasing concentrations of either drug progressively lengthen the lag phase and reduce the growth rate. The latter, however, never reaches zero, as it does in presence of other antiseptics.

At a certain stage during growth in presence of the sulphonamide there may be a transition from a slower to a more rapid rate of multiplication. This has been shown to be due to an adaptation of the bacteria.

After thirty passages through media containing sulphonamide an immunity has developed which is almost complete: it is neither specific to a particular sulphonamide, nor reversible by passage through the normal medium. The growth rate may reach that found in sulphonamide free media. To explain this it is assumed that the cells develop enzymes which produce a sulphonamide antagonist. The establishment of this complete immunity is slow and complex. In the early stages of training the adaptation is specific to one drug, easily lost, and partial, in that the growth rate is markedly less than normal. The immunity attained after one or two passages through the sulphonamide medium is of a different kind from that developed later, and can be interpreted as the shortening of the lag of an alternative growth mechanism which is more resistant to sulphonamides than that normally concerned.

The physico-chemical basis of the adaptive process is considered.

*Physical Chemistry Laboratory,
Oxford University.*

GENERAL DISCUSSION

Prof. Rideal said: Has Mr. Lodge had any evidence of the treated bacteria which showed abnormal type of growth reverting to the normal pattern when put back into normal media for several generations. I remember that during the last war I carried out a few experiments in the Somme valley on the fermentation of sugars by *B.-coli* and found that I could modify the fermentative properties of *B.-coli* for various sugars by treatment with hypochlorite. In this case the recovery of fermentative powers on sub-incubation was not achieved.

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THE SOVIET SCIENTISTS ANTIFASCIST COMMITTEE SENDING SOVIET SCIENTISTS' MESSAGE OF PROTEST AGAINST GERMAN ATROCITIES.

Cabled to the Faraday Society, and received 10th December, 1943.

The big victories of the Red Army have made 1943 an outstanding year. Beginning with Stalingrad, hundreds of towns have been regained from the Germans, amongst them mother Russian cities, and Kiev, the capital of the Ukraine. The Red Army has liberated the whole of the Ukraine lying eastward of the Dnieper, and is to-day fighting fierce and bloody battles westward of the river.

We Soviet scientists express our joy at the approaching end of the destruction wrought towards our country, and the end of the massacre and unexampled torture of Soviet citizens in occupied territories. As the Red Army advances westward our wrath increases, for we learn of countless savage crimes committed by German officers and men. Wherever the German army has been it has brought death and slavery to the people, and destruction of culture.

The Soviet writer, Alexei Tolstoy, member of the Academy of Sciences, U.S.S.R., visited the North Caucasian towns of Stavropol, Georgievsk, Kislovodsk, Essentuki, Mineralniye Vody, Zheleznovodsk, Teberda, the town of Krasnodar in the Kuban, and the city of Kharkov in the Ukraine, and everywhere he personally established the facts concerning the monstrous crimes of the Germans and the massacre of the population. An anti-tank ditch near Mineralniye Vody was opened before the eyes of Academician Tolstoy. In the ditch lay the bodies of 6000 Soviet citizens—many women, children, and aged people amongst them—who had been brutally shot by the Germans. In the city of Kharkov huge pits were opened in the presence of Alexei Tolstoy, and here lay the bodies of 12,000 Soviet citizens, many of them women and children.

Gestapo prisons were established wherever the Germans went, and behind their walls the butchers tortured their victims. The terror reigned throughout the occupied territory. The Soviet people were placed beyond the protection of law.

Every soldier of the German army is corrupted by banditry. He may, with the approval of his superiors, loot and murder Soviet people.

Professor Nikolai Burdenko, member of the Academy of Sciences, U.S.S.R., personally investigated the crimes of the Germans in the city and district of Orel. In addition to inflicting tremendous material losses on the people of the Orel district, the Germans murdered large numbers of citizens. In one graveyard under the city walls the bodies of 5000 victims of Hitler's tyranny were found. The Germans systematically murdered prisoners of war in their camps and prison hospitals where Red Army men were kept.

Academician Burdenko says in his report :—

"The picture which the eye saw was beyond all effort of the imagination. Joy at seeing the liberated peoples was darkened by that which is impressed on their features. This was something to make one ask its cause. The sufferings they had experienced apparently placed on them the sign of death in life. I had these people under my observation for three days. I bound up their injuries and arranged their evacuation, but still the psychological stupor did not change. Something similar is expressed in the faces of doctors during the first few days. People died in camps from disease and hunger and beatings. They died in hospital and in prison

from wound infections, from sepsis, and from hunger. Civilians perished from the shootings which took place in prison yards, with true German punctuality on Tuesdays and Fridays."

Burdenko also directed the investigation of German crimes in the town of Smolensk. In places in Smolensk and its environs which his commission investigated, they found the bodies of 135,000 Soviet citizens who were murdered or who died during the 26 months the Germans were near the town.

Vladimir Obraztsov and Boris Keller, members of our Academy, and Professor Vsevolod Durdenevsky of Moscow University, also saw the marks of the German's monstrous crimes, amongst them crimes against science and culture.

When they retreated from Smolensk, the Germans burned down the teaching, nutritional, and agricultural institutes, destroyed the finance, co-operative, and railway technical institutes, and the institute of telegraph and telephone communications. The Germans looted valuable collections from Smolensk museums. They blew up buildings devoted to museums, art, and history, and ruined almost all the churches, fine old monuments of Russian architecture. Academician Alexei Tolstoy also noted that the Germans, as they retreated from the towns, systematically blew up or burnt schools, scientific institutions, theatres, and museums.

In the town of Staline the Germans wrecked the medical institute and burned down all the buildings of the industrial institute where 15,000 students studied. Fearing encirclement, the Germans fled from Kiev in panic, and therefore did not have time to blow up many buildings and set fire to the city. Nevertheless, they managed to blow up and burn a number of large buildings, amongst them Kiev University, with its rich library, museums, laboratories. The German army looted all the Kiev museums, libraries, archives, laboratories, and research institutions. Academician Alexander Palladin, vice-president of the Ukrainian Academy of Sciences, bears witness to all these German crimes. Professor Alexander Brodsky, member of the Ukrainian Academy of Sciences, bears witness that the Germans blew up and burned the mining institute, with its huge library, at the University Institute of Applied Chemistry, and that they looted and destroyed a number of other research institutes at Dnepropetrovsk. Professor Peter Budnikov, member of the Ukrainian Academy, who visited Kharkov, states that the Germans destroyed the Institute of Applied Chemistry, of Electrotechnical Engineering, and other institutes.

At Poltava, Zaporozhye, Chernigov, and other towns that have been liberated from the Germans, we found colleges, libraries, and schools destroyed.

We learn from surviving inhabitants that the looting of temporarily occupied towns was organised by the German Government, and directed by German officials or army officers. A tragic fate awaited intellectuals who remained behind in German-occupied territory. Professor Tereschenko, who lived in Kharkov during the German occupation, made the following statement:—

"During two years of fascist slavery many professors and scientific workers perished. Some were shot by the Germans, others died of starvation. Academician Beketov, honoured Art-worker Burachek, Professors Rotkevich, Dybsky, Razdolsky, Rakhmaninov, and others, died of starvation. Those who lived through this period were treated as slaves."

On the basis of proven facts, we declare that the Germans are deliberately annihilating the scientists and intellectuals in occupied countries.

Scientists and medical workers are participating in the crimes of the German army. They invented the "murder-van," by which Soviet people were killed with carbon monoxide. It has been established by documentary evidence that German doctors have killed children by pumping blood out of them.

SOVIET PROTEST AGAINST GERMAN ATROCITIES 449

Forced deportation of millions of Soviet people to Germany—in some places the entire population has been driven off—the introduction of a slave-owning regime in occupied territories, the branding of prisoners of war, and hundreds and thousands of women and children and aged, as well as those who breathed a protest—this is but a short list of the crimes committed by Hitlerite Germany.

Scientists and professional people must raise their voices in protest against these crimes. We Russian scientists are doing everything in our power to ensure that our wrathful protests are accompanied by energetic action directed towards the rout of Hitlerite Germany.

We appeal to our scientist friends and colleagues in the United States and the British Commonwealth of Nations to organise protest meetings in all large cities against the atrocities, barbaric destruction, and looting of cultural institutions by German invaders.

The criminals will be made to answer their crimes. Retribution awaits them. Let this meeting of scientists strengthen this decision of liberty-loving nations.

Signed by

V. KOMAROV, President, Academy of Sciences, U.S.S.R.

A. BOGOMOLETS, President, Ukrainian Academy of Sciences.

Members of Academy of Sciences, U.S.S.R.

N. DERZHAVIN,	P. KAPITZA,	I. VINOGRADOV.
A. TOLSTOY,	N. SEMENOV,	E. TARLE.
Y. PARNAS,	S. VAVILOV,	N. BURDENKO.
A. BAIKOV,	V. VERNADSKY,	D. MANDELSTAN.
N. ZELINSKY,	G. KRZHIZHANOVSKY,	I. BARDIN.
B. VEDENEYEV,	A. PALLADIN,	B. OBRUCHEV.
V. VOLGIN,	B. OBRAZTCOV,	P. STEPANOV.
B. KELLER,	V. RODIONOV,	L. STERN.
R. WIPPER,		

Members of Ukrainian Academy of Sciences.

A. BRODSKY.	P. BUDNIKOV.
G. PROSKURA.	

Member of Belorussian Academy of Sciences.

A. ZHEBRAK.

Director of the Office of Uniflow Boiler Construction.

L. RAMZIN.

Corresponding Members, Academy of Sciences, U.S.S.R.

A. KAPUSTINSKY.

Prof. V. DURDENEV, Moscow University.

On behalf of the Soviet Scientists Antifascist Committee.

The foregoing message from our Soviet colleagues was read to those members of the Society who were present at the Annual General Meeting. They recommend that the following reply should be sent as speedily as possible:—

"THE MEMBERS OF THE FARADAY SOCIETY HAVE RECEIVED YOUR TRAGIC MESSAGE WITH HORROR AND PROFOUND SYMPATHY. THE SOCIETY WILL DO ITS UTMOST TO BRING IT TO THE NOTICE OF ALL SCIENTISTS AND INTELLECTUALS OF THE UNITED NATIONS TO THE END THAT CIVILISATION SHALL BE PROTECTED AND JUSTICE BE METED OUT TO THE BARBARIANS.

(Signed) E. K. RIDEAL (*President*).
G. S. W. MARLOW (*Secretary*)."

This reply has been sent with the authority of the Council. In accordance with the wishes of the members present at the Annual General Meeting, notice is given with this issue of the *Transactions* that the message and the reply will be considered at the adjourned Annual General Meeting. The message is of such importance that it is clearly desirable that notice of it should be given prior to the meeting.

Those present at the Annual General Meeting also desired the Secretary to publish the message and the reply in the *Transactions*, and to transmit them widely to scientific and other societies and to the technical and general press, and also to bring them to the attention of the Lord President of the Council.

It is hoped that at the Annual General Meeting members who have other suggestions for assisting our Russian colleagues will bring them forward.

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